National Library
of Canada

Bibliothèque nationale
du Canada

Canadian Theses Service

Services des thèses canadiennes

Ottawa, Canada
K1A 0N4

CANADIAN THESES

THÈSES CANADIENNES

NOTICE

The quality of this microfiche is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed.

Reproduction in full or in part of this film is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30.

AVIS

La qualité de cette microfiche dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

Les documents qui font déjà l'objet d'un droit d'auteur (articles de revue, examens publiés, etc.) ne sont pas microfilmés.

La reproduction, même partielle, de ce microfilm est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30.

THIS DISSERTATION
HAS BEEN MICROFILMED
EXACTLY AS RECEIVED

LA THÈSE A ÉTÉ
MICROFILMÉE TELLE QUE
NOUS L'AVONS REÇUE

Canada

NL-339 (r.86/06)

THE UNIVERSITY OF ALBERTA

STUDY I: ANNELATION OF β-KETO THIOLESTERS AND SYNTHETIC APPLICATION

STUDY II: STUDIES ON THE TOTAL SYNTHESIS OF α-PATCHOULENE

BY

Ⓒ LI-KANG HO

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
SPRING, 1986

Permission has been granted to the National Library of Canada to microfilm this thesis and to lend or sell copies of the film.

The author (copyright owner) has reserved other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without his/her written permission.

L'autorisation a été accordée à la Bibliothèque nationale du Canada de microfilmer cette thèse et de prêter ou de vendre des exemplaires du film.

L'auteur (titulaire du droit d'auteur) se réserve les autres droits de publication; ni la thèse ni de longs extraits de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation écrite.

ISBN 0-315-30330-1

THE UNIVERSITY OF ALBERTA

RELEASE FORM

NAME OF AUTHOR: LI-KANG HO

TITLE OF THESIS: STUDY I: Annelation of β-Keto Thiolesters and Synthetic Application STUDY II: Studies on the Total Synthesis of α-Patchoulene

DEGREE FOR WHICH THESIS WAS PRESENTED: Ph.D.

YEAR THIS DEGREE GRANTED: 1986

Permission is hereby granted to THE UNIVERSITY OF ALBERTA LIBRARY to reproduce single copies of this thesis and to lend or sell such copies for private, scholarly or scientific research purposes only.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

(Signed) Li-Kang Ho

PERMANENT ADDRESS:

No. 41-7 Lane 212
Hu Lin St. Taipei
Taiwan, R.O.C.

DATED Dec 6 '85 1985

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

STUDY I: ANNELATION OF β-KETO THIOLESTERS AND SYNTHETIC APPLICATION

STUDY II: STUDIES ON THE TOTAL SYNTHESIS OF α-PATCHOULENE

submitted by LI-KANG HO in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

Supervisor

Josef Takats

D. L. J. Clive

E. E. Knaus

Thomas G. Back

External Examiner

Date Nov. 28 1985

For my parents,

my wife

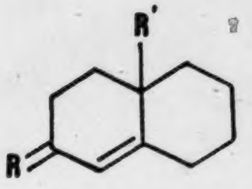
and all the people whom I respect.

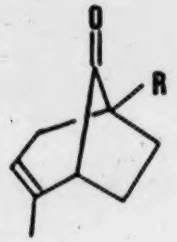
ABSTRACT

The use of β-keto thiolesters in the construction, via Michael and aldol, of fused (e.g. **1**) and bridged (e.g. **2**) ring systems possessing a functionalized substituent at the angular position has been successfully studied. Some synthetic applications of the annelation procedure have also been demonstrated including: selective reduction of the thiolester group (e.g. **2**→**3**) with Ra-Ni; the concomitant removal of ketone carbonyl and reduction of thiolester to the alcohol level via thioketal intermediate (e.g. **1**→**4**→**5**) using Ra-Ni; and the direct conversion of the ketone carbonyl to a gem-dimethyl group (e.g. **1**→**6**) using lithium dimethylcuprate. In the latter unprecedented reaction, the involvement of a lactone intermediate such as **7** was concluded based on a mechanistic investigation. This compound was shown to couple readily with lithium dimethylcuprate to give acid **6**. Extrapolation of this finding suggested that allylic pivalates might possess interesting properties in coupling with organocuprates. Indeed the experimental results showed that allylic pivalates coupled with both lithium and magnesium organocopper reagents with high efficiency. Interestingly, a complementary mode of regioselectivity was displayed by these two types of reagents. With lithium diorgano-

cuprates, the general mode is the displacement at the α-carbon resulting in the predominant formation of the "S_N2"-type products. On the other hand, the major product obtained by the use of the magnesium organocopper reagents, RMgX-CuI (2:1), was found to be consistently of the "S_N2'"-type resulting from γ-attack. For example, the reaction of compound **8** with n-BuMgBr-CuI (2:1) gave dienes **9** and **10** in a ratio of 11:1, while the latter was formed as the only product when lithium di-n-butylcuprate was used. These results are discussed in Study I of this thesis.

Study II describes the preparation of the optically active keto alcohol **11**, a potential intermediate towards the total synthesis of α-patchoulene (**12**), starting from ℓ-10-camphorsulfonic acid ammonium salt (**13**). Treatment of (**13**) with fused potassium hydroxide gave (-)-camphorlenic acid (**14**) which was converted to the corresponding ketone **15** with ethyllithium. Photooxygenation of ketone **15** using tetraphenylporphine as a sensitizer in the presence of acetic anhydride and 4-dimethylaminopyridine gave rise to enedione **16** which underwent cyclization to give ketone **17** upon treatment with methanolic potassium carbonate. Epoxidation of ketone **17** with m-chloroperbenzoic acid followed by rearrangement of the resulting epoxide **18** using stannic chloride as a catalyst afforded diketo alcohol **19**. This compound was subjected to treatment with triethylamine, 4-dimethylaminopyridine and trimethylsilyl chloride. Selective reduction of the resulting silyl ether **20** with lithium tri-_t_-butoxyaluminum hydride furnished keto alcohol **11**.





1 R = O; R' = COSEt

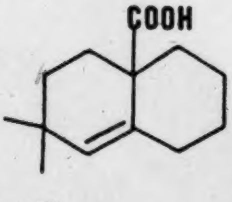
4 R = SCH_2CH_2S;

R' = COSEt

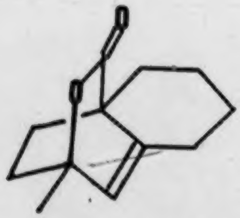
5 R = H_2 ; R' = CH_2OH

2 R = COSEt

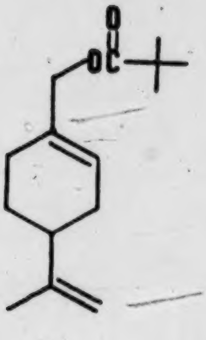
3 R = CH_2OH



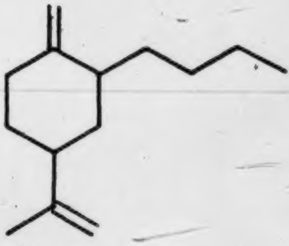
6



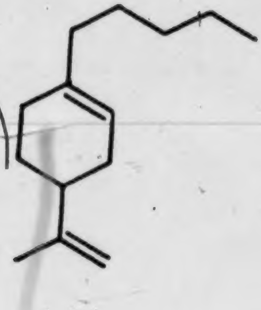
7



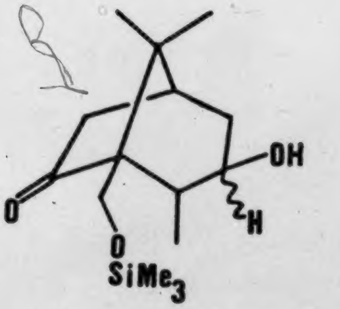
8



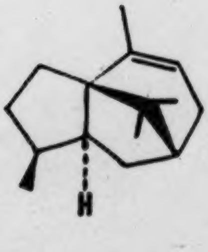
9



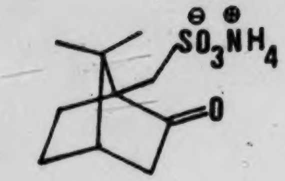
10


OH
O
H
O
SiMe3

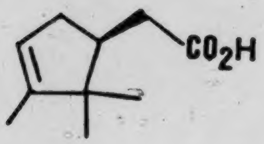
11



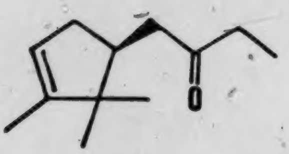
12



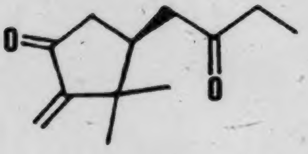
13



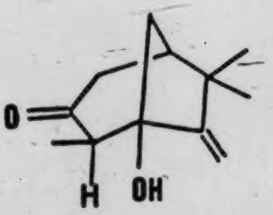
14



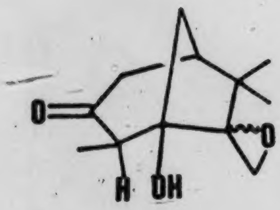
15



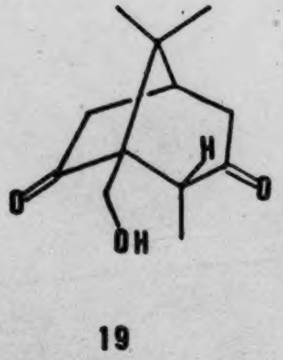
16



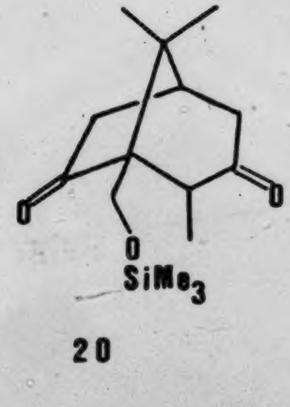
17



18



19



20

ACKNOWLEDGEMENTS

I would like to express my utmost gratitude to Professor Hsing-Jang Liu, my research supervisor, for his patient guidance and inspiring teaching throughout my study at the University of Alberta. He not only taught me the importance of organic chemistry, but also gave me tremendous help when I needed. This thesis could not have been finished without his corrections and suggestions.

My heart-felt gratitude also goes to the technical staff of this department for recording all the spectral data as well as microanalyses.

I would also like to thank Ms. Diane Dowhaniuk for typing my thesis, Dr. H. Wynn and Ms. V. Wiszniewski for their kind help in proof reading.

During my extended stay in Canada has been made enjoyable by many Canadian friends. For this I am especially indebted to Dr. Liu, and members of his family and friends of the Taiwan Universities' Alumni Association, Alberta Chapter, in Edmonton.

This study was financially supported by University of Alberta teaching assistantship and research assistantship, for which I express my sincere thanks.

TABLE OF CONTENTS

PAGE

ABSTRACT.....................................5

ACKNOWLEDGEMENTS.............................11

LIST OF TABLES...............................14

LIST OF SCHEMES..............................15

LIST OF FORMULAS.............................16

CHAPTER

STUDY I. Annelation of β-Keto Thiolesters and Synthetic Application 1

INTRODUCTION.................................2

RESULTS AND DISCUSSION.......................19

1. Michael Addition of β-Keto Thiolesters to α,β-unsaturated Carbonyl Compounds.....................................19
2. Cyclization of the Michael Adducts........26
3. Some Synthetic Applications of the Annelation Products.......................38
4. Coupling of Allylic Pivalates with Lithium and Magnesium Organocopper Reagents...................................62

EXPERIMENTAL.................................83

Table of Contents (continued):

PAGE

STUDY II. Studies on the Total Synthesis of α-Patchoulene.............................146

INTRODUCTION.................................147

RESULTS AND DISCUSSION.......................161

A. Michael-Aldol Approach....................161

B. The Rearrangement Approach................172

EXPERIMENTAL.................................202

REFERENCES...................................222

LIST OF TABLES

PAGE

TABLE

I. Michael addition of β-keto thiolesters to conjugated enones....28

II. Cyclization of the Michael adducts....39

III. Raney-nickel reduction of the bridged enones....45

IV. Thioketalization of enones and reduction of thioketal with Raney-nickel....51

V. Coupling of allylic pivalates with lithium and magnesium organocopper reagents....66

VI. Coupling of farnesyl pivalate **88** with lithium dimethylcuprate at various temperatures....71

LIST OF SCHEMES

PAGE

STUDY I.

SCHEME 1....................................21
SCHEME 2....................................35
SCHEME 3....................................55

STUDY II.

SCHEME 1....................................154
SCHEME 2....................................156
SCHEME 3....................................157
SCHEME 4....................................158
SCHEME 5....................................166
SCHEME 6....................................170
SCHEME 7....................................173
SCHEME 8....................................178
SCHEME 9....................................184
SCHEME 10...................................187
SCHEME 11...................................189
SCHEME 12...................................197

LIST OF FORMULAS

PAGE

STUDY I.

Formula 1..............................5
Formulas 2 to 7..............................6
Formulas 8 to 10 and 12..............................7
Formulas 11 and 13 to 16..............................8
Formulas 17 to 20..............................12
Formulas 21 to 24..............................15
Formulas 25 to 26..............................16
Formulas 27 to 28..............................17
Formulas 29 to 32a..............................21
Formulas 32 to 38..............................27
Formulas 39 to 46..............................34
Formulas 47 to 49..............................35
Formulas 50 to 51..............................37
Formulas 52 to 57..............................44
Formulas 58 to 64..............................49
Formulas 65 to 67..............................53
Formulas 68 to 73..............................55
Formulas 74 to 76..............................57
Formulas 77 to 82..............................60
Formulas 83 to 84..............................64
Formulas 85 to 97..............................66
Formulas 98 to 107..............................67

List of Formulas (continued):

PAGE

Formulas 86a to 87a............................69

Formulas 96a to 97a............................73

Formulas 105a to 107a..........................77

Formulas 108 to 110............................80

Formulas 111 to 112............................82

STUDY II.

Formulas 1 to 3...............................151

Formulas 4 to 9...............................152

Formulas 10 to 11.............................153

Formula 12 154

Formula 13 155

Formulas 14 to 15b............................156

Formulas 16 to 17.............................158

Formulas 18 to 23.............................159

Formulas 24 to 25.............................160

Formulas 26 to 31.............................164

Formulas 32 to 33.............................168

Formulas 34 to 36.............................170

Formulas 37 to 38.............................173

Formula 39 175

Formulas 40 to 41.............................181

Formulas 42 to 43.............................186

List of Formulas (continued)

PAGE

Formula 44 187
Formulas 45 to 46...........................193
Formulas 47 to 48...........................197
Formulas 49 to 50...........................198
Formulas 51 to 53...........................201

STUDY I

Annelation of β-Keto Thiolesters and Synthetic Application

INTRODUCTION

The isolation of the first documented thiolester was described more than a century ago by Muhler[1] who observed that the reaction of acetyl chloride and ethyl mercaptan gave ethyl thiolacetate. In the ensuing years, several other synthetic methods were described for the formation of thiolesters.[2] It was, however, not until 1946, some seventy years after its first discovery, that the synthetic utility of the thiolester functionality was realized. Apparently inspired by the then new observations of the simultaneous desulfurizing and reducing action[3,4] of Raney nickel,[5] Wolfrom and Karabinos,[6] and Prelog _et al_.[7,8] independently and concurrently studied the Raney nickel reduction of thiolesters. The former group found that the reduction of thiolesters gave rise to the corresponding aldehydes while the latter school noted the formation of primary alcohols as the end products. Further studies by Levin and coworkers[8,10] in 1948 confirmed both observations and showed that the discrepancy in previous findings was apparently due to the degree of reactivity of the Raney nickel used; with a standard Raney nickel catalyst using normal reaction conditions, alcohols were produced from the corresponding thiolesters, whereas, with deactivated

Raney-nickel, the aldehydes were formed. These results are summarized in Eq. 1.

Since the early 1960's the interest in thiolesters has grown rapidly due to the recognition of their potential as useful intermediates in organic synthesis. In a relatively short period of time, a large number of new synthetic methods based on the thiolester group have been developed to facilitate the formation of carbon-carbon bonds and the transformation of functionalities, often under mild and specific reaction conditions. As well, new and improved methods for the preparation of this class of compounds have emerged.

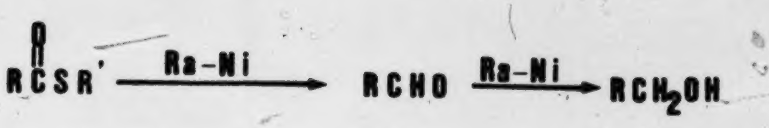
Several preparative methods were reported by Mukaiyama, *et al.* They showed that carboxylic acids could be directly converted to the respective thiolesters by treatment either with triphenylphosphine and a disulfide (Eq. 2)[11] or with an onium salt of azaarenes **1** in the presence of a tertiary amine and a thiol (Eq. 3).[12] Alternatively, they found that thiolesters could be prepared by transesterification of *O*-esters with trimethylsilyl sulfides under aluminum chloride catalysis (Eq. 4).[13]

Phosphorus-containing reagents have been used extensively to activate carboxylic acids. In the presence of a thiol, the resulting mixed anhydrides **2** were shown to undergo further reaction to give thiolesters in accordance with the general equation (Eq. 5). Activating agents effectively applied include diphenyl phosphorazidate (**3**),[14] diethyl phosphorocyanidate (**4**),[15] N,N-dimethylphosphoramidic dichloride (**5**),[16] phenylphosphorodichloridate (**6**),[17,18] and N,N-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride (**7**).[19]

It has also been shown[20-22] that the mixed anhydrides (or acid chlorides) react effectively with thallous 2-methylpropane-2-thiolate to give S-t-butyl thiolesters (Eq. 6).

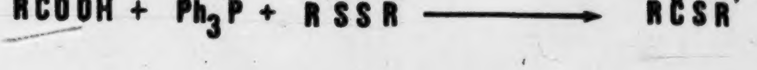
Other activating agents useful for the conversion of carboxylic acids to thiolesters include 1-fluoro-2,4,6-trinitrobenzene (**8**)[23] which converts carboxylic acids to active derivatives **9** (Eq. 7), carbonyl diimidazole (**10**) and carbonyl 1,2,4-triazole (**11**).[24] When subjected to reactions with carboxylic acids, the latter two reagents gave rise to highly reactive carboxylic acid imidazolides **12** (Eq. 8) and 1,2,4-triazolides **13** (Eq. 9) respectively. 2-Mercaptobenzoxazole **14** has also been used as an activating agent which effects the conversion of carboxylic acids to S-acyl and N-acyl derivatives **15** and **16** (Eq. 10)[25] as reactive intermediates.

Associated with the thiolester group are two important attributes which make this functionality highly



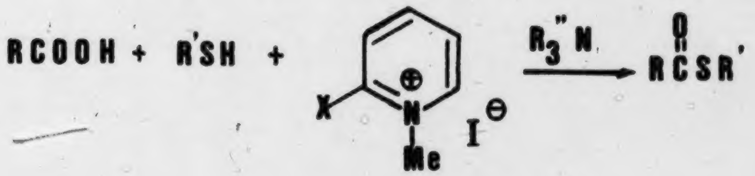
$$\mathrm{R\overset{\overset{O}{\|}}{C}SR'} \xrightarrow{\mathrm{Ra-Ni}} \mathrm{RCHO} \xrightarrow{\mathrm{Ra-Ni}} \mathrm{RCH_2OH}$$

(Eq. 1)



$$\mathrm{RCOOH + Ph_3P + R'SSR'} \longrightarrow \mathrm{R\overset{\overset{O}{\|}}{C}SR'}$$

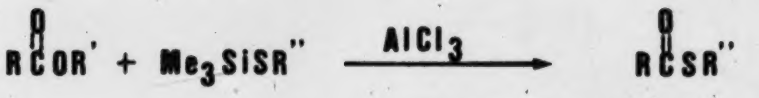
(Eq. 2)



$$\mathrm{RCOOH + R'SH} + \mathbf{1} \xrightarrow{\mathrm{R_3''N}} \mathrm{R\overset{\overset{O}{\|}}{C}SR'}$$

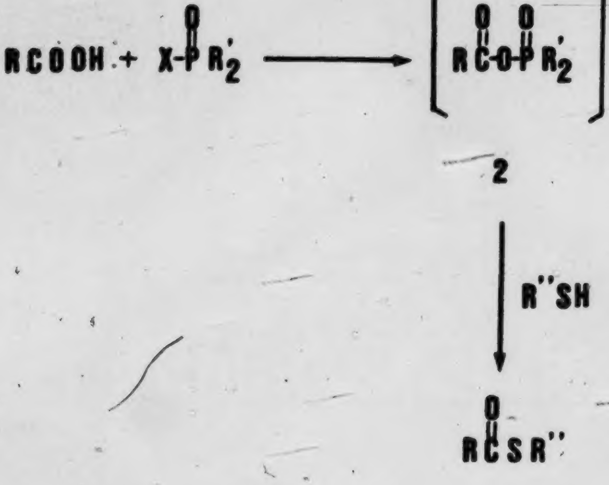
(Eq. 3)

1 X = F, Cl, Br

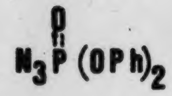


$$\mathrm{R\overset{\overset{O}{\|}}{C}OR' + Me_3SiSR''} \xrightarrow{\mathrm{AlCl_3}} \mathrm{R\overset{\overset{O}{\|}}{C}SR''}$$

(Eq. 4)

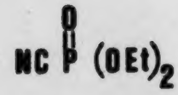


$$\mathrm{RCOOH} + \mathrm{X}\text{-}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{P}}\mathrm{R'_2} \longrightarrow \underset{\mathbf{2}}{\left[\mathrm{R}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{O}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{P}}\mathrm{R'_2}\right]} \xrightarrow{\mathrm{R''SH}} \mathrm{R}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{SR''} \qquad \text{(Eq. 5)}$$



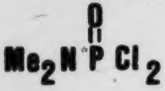
$$\mathrm{N_3}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{P}}\mathrm{(OPh)_2}$$

3



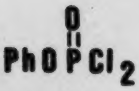
$$\mathrm{NC}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{P}}\mathrm{(OEt)_2}$$

4



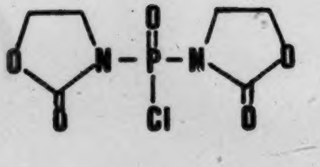
$$\mathrm{Me_2N}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{P}}\mathrm{Cl_2}$$

5

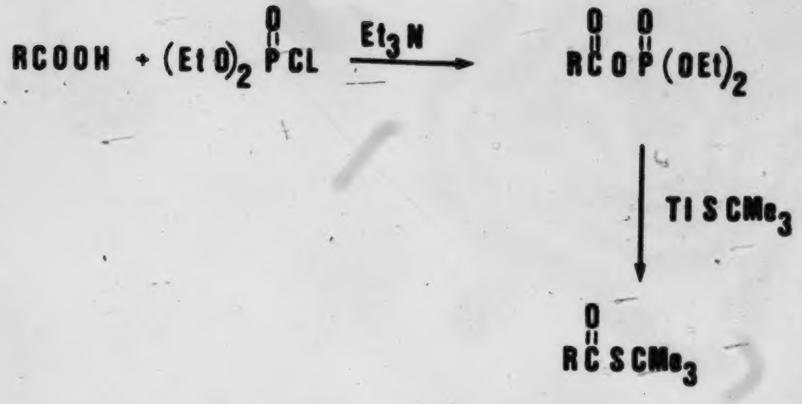


$$\mathrm{PhO}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{P}}\mathrm{Cl_2}$$

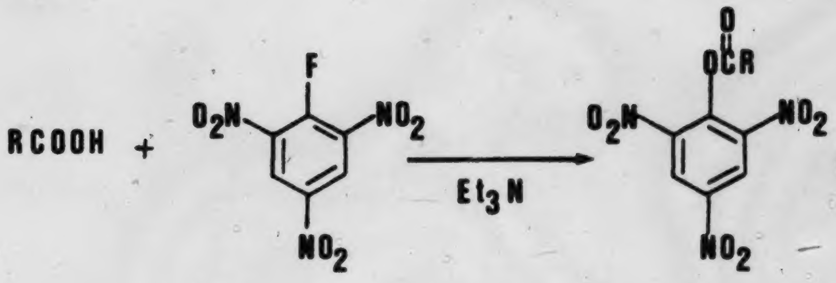
6



7



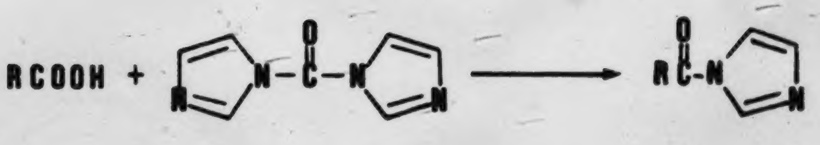
(Eq. 6)



(Eq. 7)

8

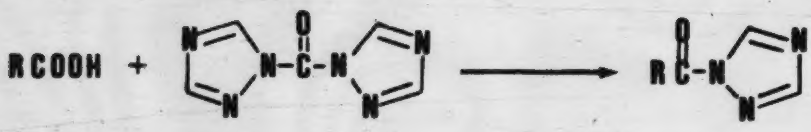
9



(Eq. 8)

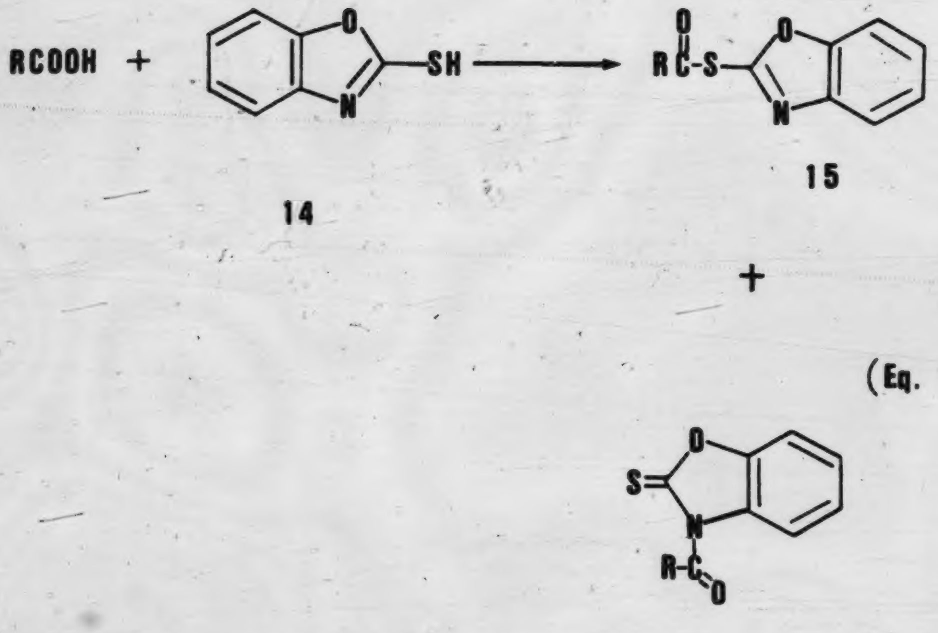
10

12



11 13

(Eq. 9)



14

15

(Eq. 10)

16

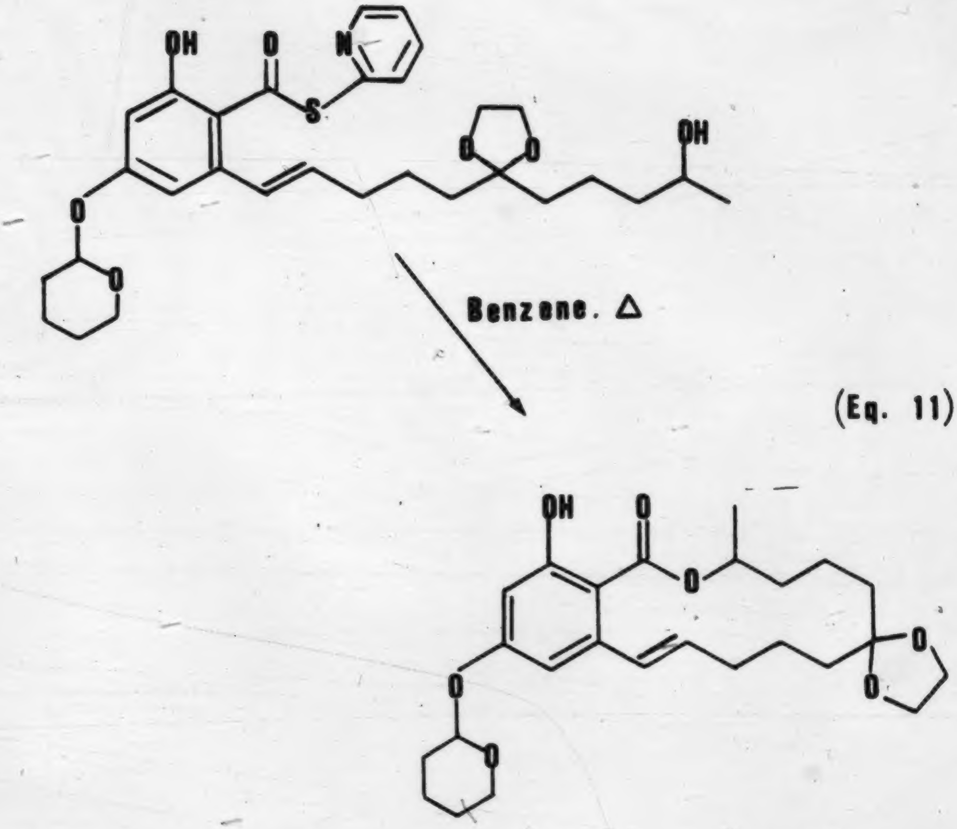
useful in organic synthesis. Thiolesters are generally stable compounds and can be handled without special precautions. When subjected to reactions under a specific set of conditions, however, a high degree of reactivity can be achieved due to the following properties of the thiolester moiety.

1. As discussed previously, the carbon-sulfur bond is prone to reductive cleavage with Raney nickel.
2. Mercaptide is a good leaving group. Furthermore, the sulfur atom can easily form complexes with a number of metal cations such as Hg^{++}, Ag^{+}, and Cu^{+}. Thus, the departing ability of the mercaptide group can be easily enhanced with the assistance of a suitable metal ion.
3. The acyl group of thiolesters is much more electrophilic than that of the corresponding _O_-esters. Consequently, nucleophilic addition takes place more readily with thiolesters.
4. The acidity of thiolesters is considered to be quite close to that of ketones ($pk_a \sim 19$) and is certainly much greater than that of _O_-esters ($pk_a \sim 25$). Hence, the deprotonation of thiolesters possessing one or more enolizable α-protons can be effected under rather mild conditions.

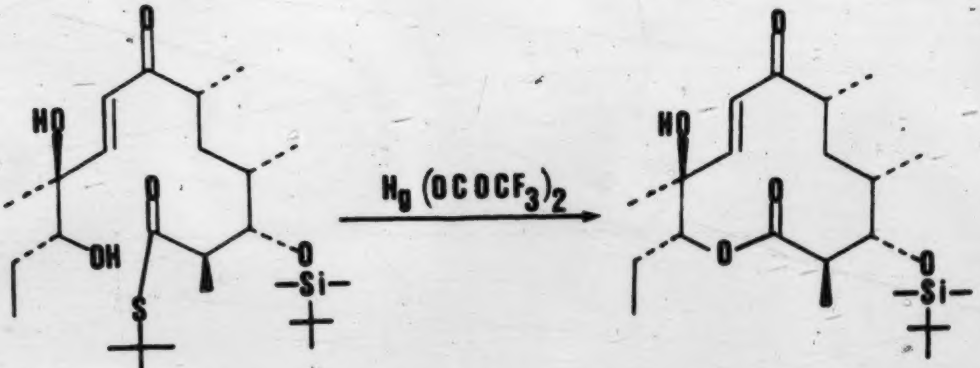
Other than the reductive desulfurization to give aldehydes and alcohols, thiolesters have found extensive use as reactive intermediates to facilitate the formation of lactone rings of various sizes.[26-30] Examples are to be found in Eq. 11[31] and 12.[32] These methods have been successfully applied to the total synthesis of many macrolides, such as zearalenone (**17**),[26] methymycin (**18**),[32] brefeldin A (**19**),[26] and enterobactin (**20**),[31] possessing a broad spectrum of biological activities.

Another application of thiolesters to the synthesis of biologically important molecules has been successfully explored recently by Woodward et al.[33] They found that, upon heating in toluene, β-lactam thiolacetate **21** underwent cyclization via an intramolecular Wittig-type reaction to give penem derivative **22** (Eq. 13), thus providing a new approach for the synthesis of β-lactam antibiotics.

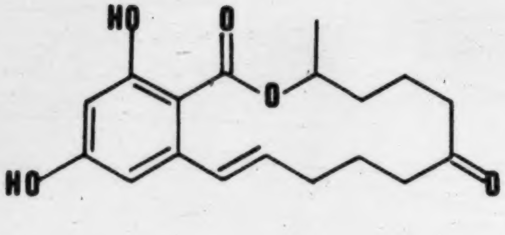
Other thiolester-based synthetic methods developed include the formation of ketones[34] with organocopper reagents (Eq. 14) and the Dieckmann condensation of dithiol diesters,[35,36] for example **23** → **24** (Eq. 15), which was shown to proceed under conditions substantially milder than those required for the standard condensation of the oxygen analogues. During the course of studies of the



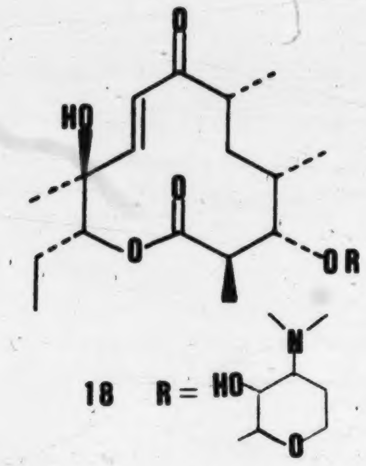
(Eq. 11)



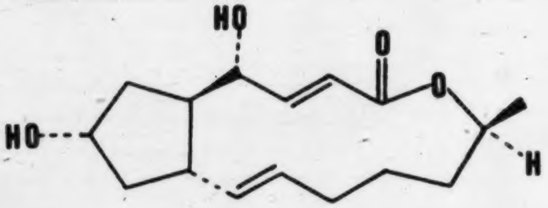
(Eq. 12)


HO
O
O
HO
O

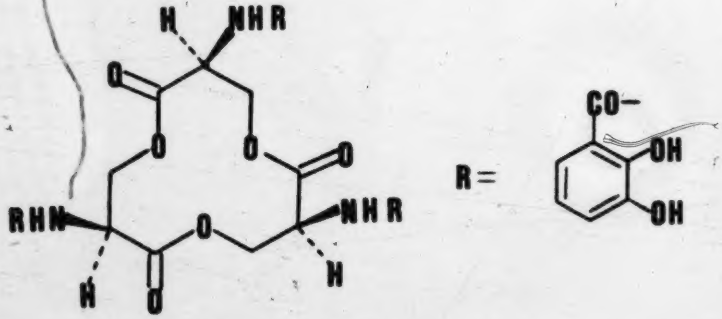
17


O
HO
O
O
OR
N
R =
HO
O

18


HO
O
O
HO
H

19


H
NHR
O
O
O
O
RHN
O
NHR
H
O
H
R =
CO–
OH
OH

20

latter reactions, it was also observed that β-keto thiolesters, unlike simple thiolesters, underwent dealkylthiocarbonylation to give the corresponding ketones (e.g. **24** → **25** (Eq. 16)) when subjected to Raney nickel treatment. It was due to this interesting accidental finding that a research project was initiated in our laboratory to study the utility of thiolesters in organic synthesis and over a period of six years, several methods have been developed accordingly. The ease of removal from β-keto thiolesters with Raney nickel makes the thiolester group an attractive activating group for α-substitution of ketones. Accordingly, a general method was developed for the preparation of β-keto thiolesters via methylthiocarbonylation of ketones[37] using S,S'-dimethyl dithiocarbonate (Eq. 17). β-Keto thiolesters were subsequently found to undergo substitution readily with a variety of electrophiles (Eq. 18).[38] More importantly, the removal of the thiolester moiety from the highly substituted β-keto thiolesters (Eq. 18) was shown to be equally facile with Raney nickel under virtually neutral conditions.[38]

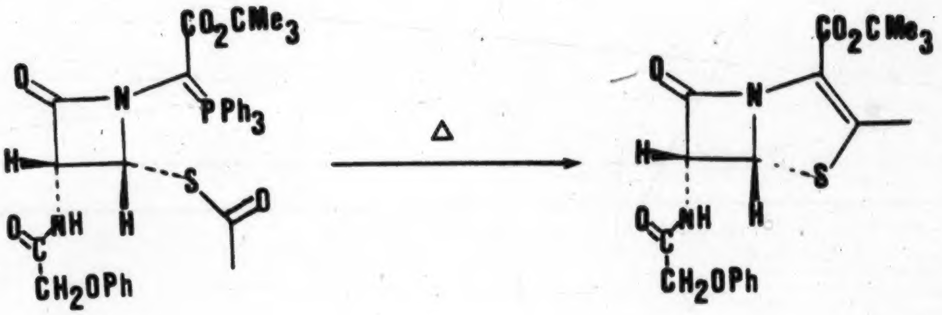
Based on the observed unusual reactivity of the β-keto thiolester moiety towards Raney nickel, the feasibility of using S,S'-diethyl dithiomalonate (**26**) as an ethanol carbanion equivalent in substitution reactions

(Eq. 19)[35] and Michael additions (Eq. 20)[39] has also been realized experimentally.

Due to its high electrophilicity, the thiolester group is susceptible to reduction with the mild reducing agent sodium borohydride which does not reduce commonly encountered stable acid derivatives such as _O_-esters, amides, and nitriles. This was first observed by Fujita and coworkers on the highly activated thiolesters **27** (Eq. 21) derived from 2-mercaptothiazoline[40] but later it was shown in our laboratory that ordinary thiolesters could also be reduced to the alcohol level.

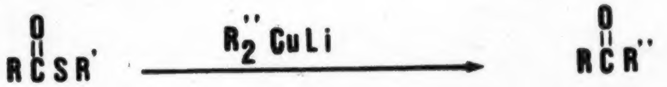
The ease of reduction of the thiolester group with sodium borohydride provides a number of interesting possibilities for its use as a latent hydroxymethyl unit in synthesis, especially when such a unit with or without protection can not be directly involved in a desired transformation. For instance, cyanothiolacetate **28** can be considered as a masked β-hydroxypropionitrile unit. Its application to the synthesis of β-hydroxypropionitriles and acrylonitriles (Eq. 22) has recently been demonstrated.[41]

As a part of the broad research project directed towards the synthetic applications of thiolesters, we have examined the annelation reactions of β-keto thiolesters as



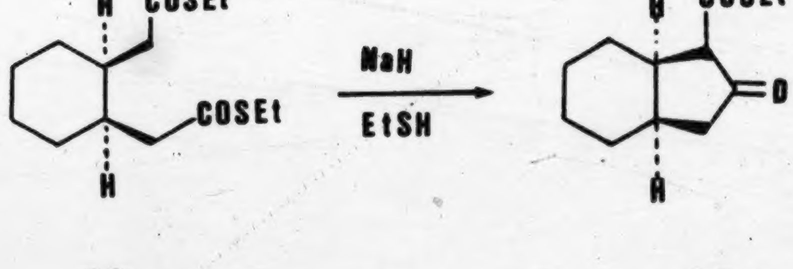
CO₂CMe₃
PPh₃
Δ
CH₂OPh

21 22 (Eq. 13)



$$\mathrm{R\overset{O}{\overset{\|}{C}}SR'} \xrightarrow{\mathrm{R''_2CuLi}} \mathrm{R\overset{O}{\overset{\|}{C}}R''}$$

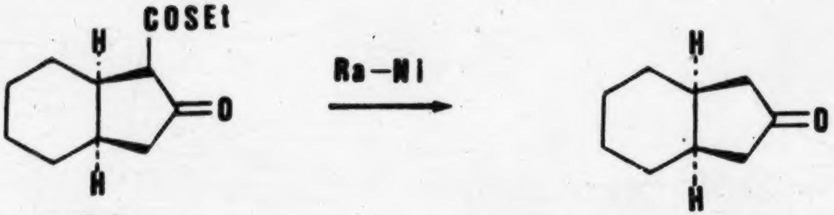
(Eq. 14)



COSEt
NaH
EtSH

(Eq. 15)

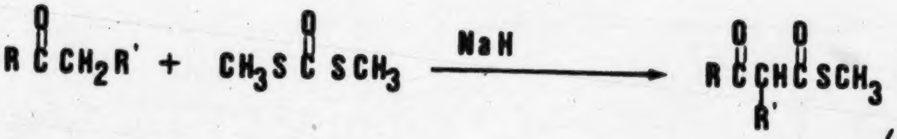
23 24



24

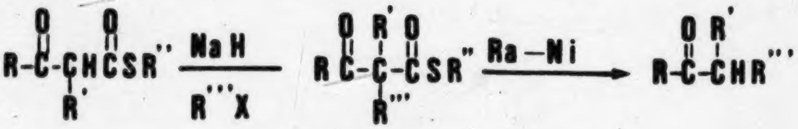
25

(Eq. 16)



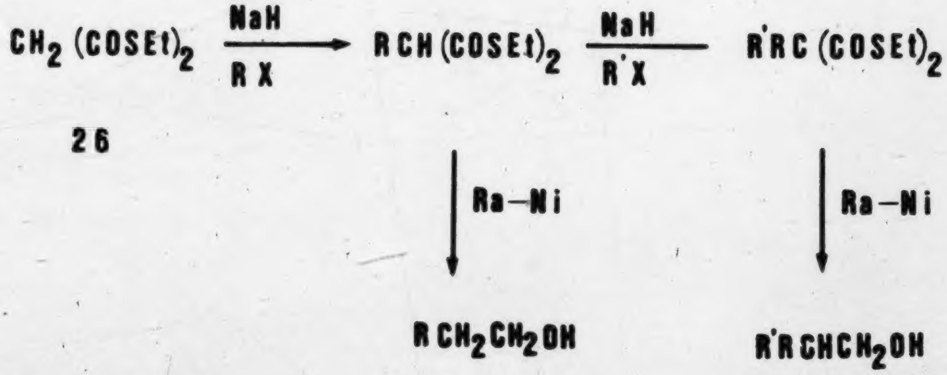
$$\mathrm{R\overset{O}{\overset{\|}{C}}CH_2R' + CH_3S\overset{O}{\overset{\|}{C}}SCH_3 \xrightarrow{NaH} R\overset{O}{\overset{\|}{C}}\underset{R'}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}SCH_3}$$

(Eq. 17)



$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\underset{R'}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}SR'' \xrightarrow[R'''X]{NaH} R\overset{O}{\overset{\|}{C}}{-}\underset{R'''}{\underset{|}{\overset{R'}{\overset{|}{C}}}}{-}\overset{O}{\overset{\|}{C}}SR'' \xrightarrow{Ra-Ni} R{-}\overset{O}{\overset{\|}{C}}{-}\overset{R'}{\overset{|}{C}}HR'''}$$

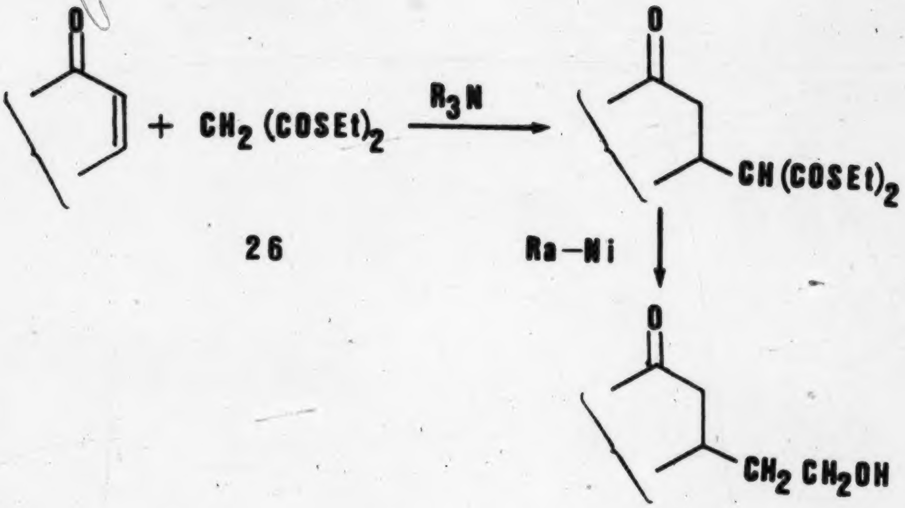
(Eq. 18)



$$\begin{tikzcd}
\mathrm{CH_2(COSEt)_2} \arrow[r, "\mathrm{NaH}", "\mathrm{RX}"'] & \mathrm{RCH(COSEt)_2} \arrow[r, "\mathrm{NaH}", "\mathrm{R'X}"'] \arrow[d, "\mathrm{Ra-Ni}"] & \mathrm{R'RC(COSEt)_2} \arrow[d, "\mathrm{Ra-Ni}"] \\
 & \mathrm{RCH_2CH_2OH} & \mathrm{R'RCHCH_2OH}
\end{tikzcd}$$

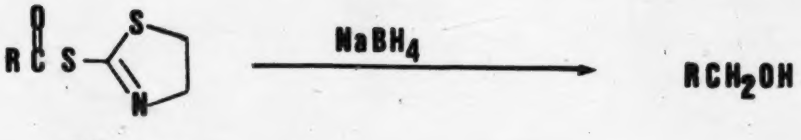
26

(Eq. 19)


R3N
Ra–Ni
CH(COSEt)2
CH2CH2OH

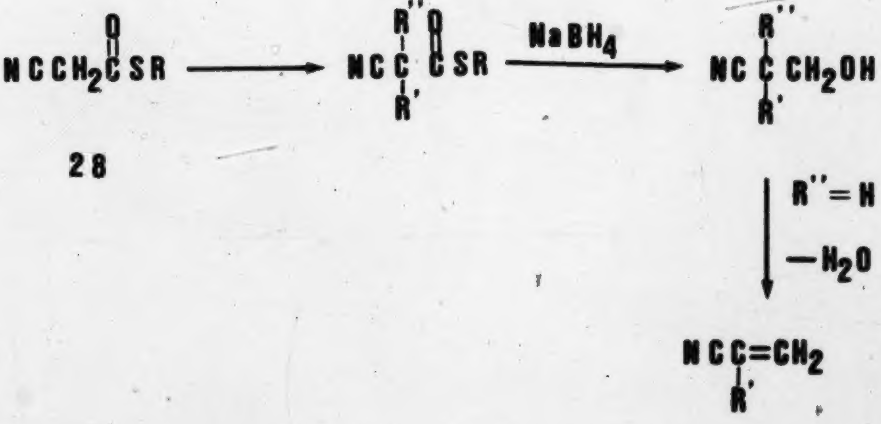
26

(Eq. 20)


NaBH4
RCH2OH

27

(Eq. 21)



$$NCCH_2\overset{O}{\overset{\|}{C}}SR \longrightarrow NC\underset{R'}{\overset{R''}{C}}\,\overset{O}{\overset{\|}{C}}SR \xrightarrow{NaBH_4} NC\underset{R'}{\overset{R''}{C}}CH_2OH \xrightarrow[-H_2O]{R''=H} NC\underset{R'}{C}{=}CH_2$$

28

(Eq. 22)

well as the chemistry of the reaction products. Results are detailed in this chapter.

During the course of the studies, an interesting coupling reaction was observed. This led to the examination of the coupling reactions of allylic pivalates with lithium and magnesium organocopper reagents. Results obtained for these studies are also discussed in this chapter.*

---

* Part of the results discussed in this chapter has been published.[42,43]

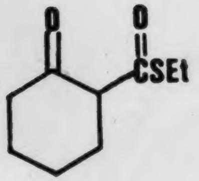
RESULTS AND DISCUSSION

Three β-keto thiolesters **29**, **30** and **31** were used for the present studies. These compounds were readily prepared according to the procedures developed in our laboratory; the first two by the Dieckmann condensation of _S,S_'-diethyl dithiolpimalate and _S,S_'-diethyl dithioladipate respectively.[44] The reactions were carried out in 1,2-dimethoxyethane at room temperature using sodium ethylmercaptide as a base. Compound **31** was synthesized by α-methylthiocarbonylation of 2-methylcyclohexanone with _S,S_'-dimethyl dithiocarbonate and sodium hydride in refluxing 1,2-dimethoxyethane.[37] An improved yield of 85% was obtained for **31** when the reaction was allowed to proceed for 12 h instead of 16 h.

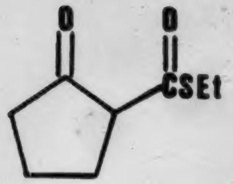
1. Michael Addition of β-Keto Thiolesters to α,β-Unsaturated Carbonyl Compounds.

The six-membered ring annelation of the β-keto thiolesters examined was carried out in all cases _via_ a two-step reaction sequence: Michael addition followed by an aldol condensation. In our initial attempts to induce the Michael reaction of β-keto thiolester **29** to methyl vinyl ketone, the use of the sodium and lithium salts **29a**, generated in situ using sodium hydride and lithium hydride respectively, was found to be completly ineffective. Under a variety of conditions, the starting material was recovered intact. These results could be attributed to the unfavorable reversible nature of the reaction (Scheme 1) due to the high stability of the anion **29a** which can also serve as an excellent leaving group. A likely solution to this problem would be to trap the incipient anion **32a** with a proton source. In assessing various solutions, the use of a tertiary amine as a base evolved as an attractive possibility. Tertiary amines are sufficiently basic to deprotonate β-keto thiolesters, which should possess acidity comparable to that of the closely related oxygen analogues ($pk_a \sim 11$), and therefore should produce a reasonable concentration of the required anion such as **29a**. Furthermore, the conjugate acid of the tertiary amine so generated is far more acidic ($pk_a \sim 10$) than a ketone ($pk_a \sim 20$) and consequently it can conveniently serve as an excellent proton source to trap the intermediate enolate ion **32a** virtually irreversibly (i.e. deprotonation).

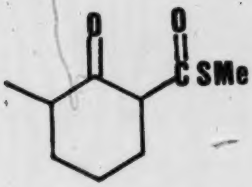
The above expectations were proven experimentally to be correct. In the presence of a tertiary amine, β-keto thiolesters were found to undergo Michael reaction readily



29

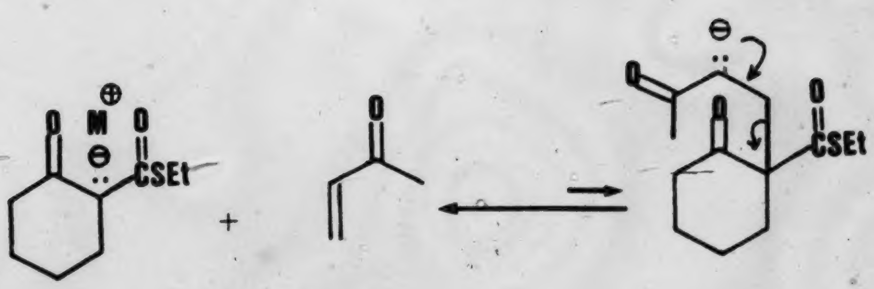


30



31

SCHEME 1



M = Li, Na

29a

32a

with α,β-unsaturated carbonyl compounds. Several amines were examined including triethylamine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,8-diazabicyclo[5.4.0]undec-7-ene, and 1,4-diazabicyclo[2.2.2]octane (DABCO). Of these, DABCO was shown to be most effective, giving consistently high yields of the products under mild conditions. In a typical experiment, DABCO and methyl vinyl ketone (1.2 equiv. each) were added to a solution of 2-ethylthiocarbonylcyclohexanone (**29**) in 1,2-dimethoxyethane (ca. 4 mL/mmol of **29**). After stirring at room temperature under a nitrogen atmosphere for 24 h, the reaction mixture was acidified with hydrochloric acid and extracted with ether. The usual work-up of the organic solution followed by column chromatography of the crude product on silica gel gave adduct **32** in quantitative yield. Compound **32** showed in the ir spectrum, absorption bands at 1712 (ketones) and 1665 cm^{-1} (thiolester). The ^{1}Hmr spectrum showed a two-proton quartet at δ 2.88 which was mutually coupled to the triplet (three protons) at δ 1.26. These signals were readily attributed to the ethyl thiolester group. In addition, a methyl singlet at δ 2.04 for the ketone side chain was also observed. The mass spectrum did not display the required molecular ion peak. However, a prominent peak was found at 195.1021 resulting from the loss of a CH_3CH_2S unit.

The reaction of **29** with ethyl vinyl ketone proceeded similarly to give adduct **33** in 88% yield. Two intense carbonyl absorption bands, a broad one at 1712 cm^{-1} and the other at 1665 cm^{-1}, were again observed in the ir spectrum. The ^{1}Hmr spectrum indicated the presence of ethyl thiolester group displaying a methylene quartet at δ 2.88 and a methyl triplet at δ 1.25, each with a coupling constant of 7 Hz. Another triplet with an 8 Hz coupling constant was also observed for the methyl group of the ketone side chain. The molecular ion in this case was sufficiently stable to be detected in the mass spectrum at m/e 270.1290 in agreement with the required molecular formula $C_{14}H_{22}O_3S$.

β-Keto thiolester **29** was also shown to react with acrolein readily at room temperature in 1,2-dimethoxyethane in the presence of DABCO. In this case, however, the reaction was found to stop proceeding after 8 h or so presumably due to the consumption of acrolein by competing processes, e.g. polymerization. To drive the reaction to completion, an additional quantity (0.5 equiv.) of acrolein was introduced and the reaction was allowed to proceed for a further period of 3 h during which time the starting material was completely consumed. The adduct **34** thus obtained in 88% yield showed, in the ^{1}Hmr spectrum, a low field triplet at δ 9.71 characteristic of the aldehydic proton. The ir spectrum displayed, in addition to the carbonyl absorptions at 1720 (ketone and aldehyde), 1680 and 1670 cm^{-1} (thiolester), two diagnostic bands at 2876 and 2732 cm^{-1} for the aldehyde group. Instead of the molecular ion peak which was not observed, the mass spectrum displayed two prominent peaks at m/e 181.0866 ($C_6H_{13}O_3$) and 153.0904 ($C_9H_{13}O_2$). These peaks could be attributed to the loss of CH_3CH_2S and $COSCH_2CH_3$ units respectively.

Under similar conditions, the Michael reaction of the five-membered β-keto thiolester **30** proceeded equally well. Treatment of **30** with methyl vinyl ketone gave rise to, in quantitative yield, diketo thiolester **35** which showed, in the ir spectrum, three distinct carbonyl absorption bands at 1744 (five-membered ketone), 1716 (sidechain ketone), and 1665 cm^{-1} (thiolester). The ^{1}Hmr spectrum confirmed the presence of a methyl ketone moiety which appeared at δ 2.04 as a singlet integrating to three protons. Other characteristic signals, apparently due to the ethyl group, appeared at δ 2.84, a two-proton quartet (J = 7 Hz), and δ 1.22, a three proton triplet (J = 7 Hz).

Using methyl and ethyl vinyl ketone and acrolein as Michael acceptors, three adducts **36**, **37**, and **38** were prepared from β-keto thiolester **31**. The reactions proceeded uneventfully. Suffice it to say that the products were all obtained in good yields (88-100%). Adduct **36** displayed three carbonyl absorption bands in the ir spectrum, two for ketones at 1718 and 1705 cm^{-1} and the remaining one at 1664 cm^{-1} for the ester group. The ^{1}Hmr spectrum showed two methyl singlets at δ 2.26 and 2.04 for the methyl thiolester and the methyl ketone moieties respectively. In addition, a doublet at δ 0.96 with a coupling constant of 7 Hz was also observed for the methyl group attached directly to the ring. The mass spectrum failed to show the expected molecular ion peak but the base peak at m/e 209.1176 ($C_{12}H_{17}O_3$) could be readily attributed to the loss of a SCH_3 unit.

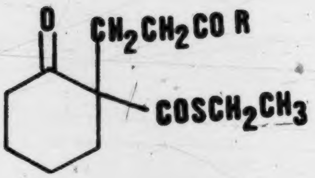
In the ir spectrum of adduct **37**, the ketone absorption bands found to superimpose at 1714 cm^{-1} while the thiolester gave an intense band at 1670 cm^{-1}. The ^{1}Hmr spectrum showed three methyl signals, a singlet at δ 2.28 for the thiolester, a triplet ($J = 8$ Hz) at δ 0.98 for the ethyl ketone grouping, and a doublet ($J = 6$ Hz) at δ 0.97 for the remaining methyl. Although the molecular ion peak was again not observed in this case, the mass spectrum lent strong support to the structural assignment by displaying two prominent ion peaks at m/e 223.1334 ($C_{13}H_{19}O_3$) and 195.1386 ($C_{12}H_{19}O_2$) due to the loss of SCH_3 and $COSCH_3$ respectively.

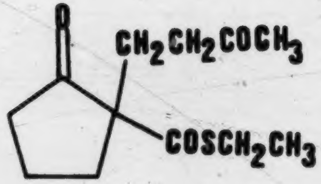
Adduct **38** obtained from β-keto thiolester **31** and acrolein as a mixture of two epimers was shown to be rather unstable. When subjected to purification by column chromatography on silica gel, a substantial deterioration of the compound was observed. The pure material, however, could be obtained satisfactorily by distillation and showed two sets of signals (*ca*. 4:1) in the ^{1}Hmr spectrum indicating the presence of two stereoisomers. Each set contained a narrowly split triplet (J = 2 Hz each) for the aldehydic proton (δ 9.69 for the major and 9.71 for the minor). The presence of the aldehyde group was confirmed by the ir spectrum which displayed characteristic absorption bands at 2862, 2720, and 1720 cm^{-1} along with those at 1708 and 1664 cm^{-1} for the ketone carbonyl and the thiolester carbonyl respectively. Further in agreement with the structural assignment, the mass spectrum exhibited the required molecular ion peak at m/e 242.0969.

The experimental results obtained for the Michael addition reactions are further compiled in Table 1.

2. Cyclization of the Michael Adducts

The Michael adducts were readily cyclized to give the octalone system under the influence of *p*-toluenesulfonic


O
CH2CH2COR
COSCH2CH3

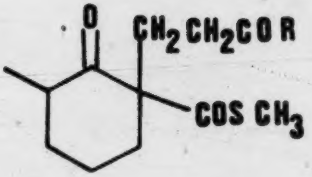

O
CH2CH2COCH3
COSCH2CH3

35

32 R = CH_3

33 R = CH_2CH_3

34 R = H

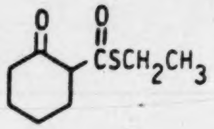
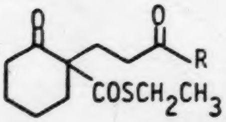
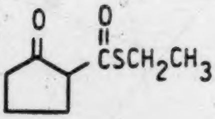
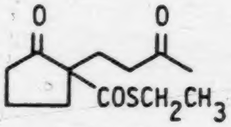
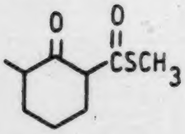
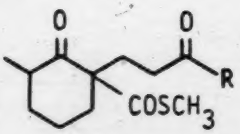

O
CH2CH2COR
COS CH3

36 R = CH_3

37 R = CH_2CH_3

38 R = H

Table 1. Michael addition of β-keto thiolesters to conjugated enones.

β-Keto Thioester	Enone	Time(h)	Product	Yield (%)
 **29**	$CH_2=CHCOCH_3$	24	 **32** R=CH_3	100
	$CH_2=CHCOCH_2CH_3$	16	**33** R=CH_2CH_3	88
	$CH_2=CHCHO$	11	**34** R=H	88
 **30**	$CH_2=CHCOCH_3$	2.5	 **35**	100
 **31**	$CH_2=CHCOCH_3$	48	 **36** R=CH_3 (two isomers)	97
	$CH_2=CHCOCH_2CH_3$	48	**37** R=CH_2CH_3 (two isomers)	100
	$CH_2=CHCHO$	12	**38** R=H (two isomers)	88

acid using a well-documented procedure.[45,46] Treatment of diketone **32** with a small amount (1/6 of **32** by weight) of p-toluenesulfonic acid in refluxing benzene with a Dean-Stark water separator for 10 h gave rise to a 98% yield of bicyclic enone **39**. Similarly, reaction of diketone **33** gave enone **40** in quantitative yield. Enone **39** showed, in the ir spectrum, three characteristic absorption bands at 1687, 1670, and 1618 cm^{-1} for the ketone carbonyl, the thiolester group, and the carbon-carbon double bond respectively. In the ^{1}Hmr spectrum, in addition to the methylene quartet ($J = 8$ Hz) at δ 2.89 and the methyl triplet ($J = 8$ Hz) at δ 1.26 characteristic for the ethyl group of the thiolester, a low field singlet appeared at δ 5.92 due to the vinylic proton attached to the newly formed enone double bond. The mass spectrum further confirmed the structural assignment showing the required molecular ion peak at 238.1030. The ir spectrum of enone **40** was found to be similar to that of compound **39**; three diagnostic absorption bands were displayed at 1675, 1612 (enone), and 1667 cm^{-1} (thiolester). The mass spectrum indicated the presence of an additional methylene unit showing a molecular ion peak at 252.1184 for the molecular formula of $C_{14}H_{20}S$. The absence of any vinylic protons was clearly indicated by the ^{1}Hmr spectrum which also displayed a three-proton singlet at δ 1.81 due to the vinylic methyl group.

The cyclization of the five-membered ring compound **35** was shown to be equally facile. Enone **41** thus obtained in 90% yield showed a narrowly coupled (J = 2 Hz) triplet at δ 5.91 for the vinylic proton in the ^{1}Hmr spectrum and a molecular ion peak at 224.0871 in the mass spectrum. In the ir spectrum, all the characteristic absorption bands were present including those at 1721 (ketone), 1670 (thiolester), and 1645 cm^{-1} (carbon-carbon double bond).

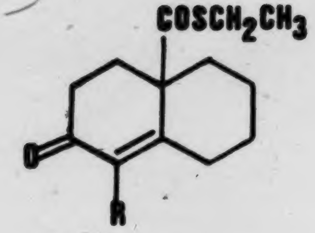
The second possible mode of aldol condensation leading to a bridged system could be effected by Marshall's modification[47] of the Wichterle reaction. The method, which effectively induces the kinetically controlled aldol cyclization, involves the use of concentrated sulfuric acid as a reagent. When diketo thiolester **32** was briefly (30 min) exposed to cold (2-4°C) concentrated sulfuric acid in benzene, the bridged enone **42** was obtained in 93% yield. The compound was readily characterized by the following spectral properties. In the mass spectrum, a molecular ion peak at 238.1026 verified its molecular composition of $C_{13}H_{18}O_2S$. The presence of the ketone and thiolester carbonyl groups were clearly indicated by the absorption bands observed at 1721 and 1669 cm^{-1} respectively in the ir spectrum. The ^{1}Hmr spectrum displayed a one-proton multiplet at δ 5.65 typical of a vinylic proton on a non-conjugated carbon-carbon double bond. This along with the appearance of a vinylic methyl signal at δ 1.70 as a doublet of doublets (J = 4, J' = 2 Hz) further confirmed the formation of the bridged system.

Similarly, under kinetically controlled conditions using sulfuric acid, the cyclization of the ethyl analog **33** furnished keto ester **43** in 95% yield. In the ^{1}Hmr spectrum of this compound, the ethyl signals of the thiolester group were observed at δ 2.84 as a quartet and δ 1.23 as a triplet, each with a coupling constant of 7 Hz. In agreement with the structure, the ^{1}Hmr spectrum also indicated the presence of a second ethyl group with the triplet (J = 8 Hz) at δ 1.01 and a vinylic proton with the multiplet at δ 5.61. Both the ir and mass spectra were in support of the structural assignment. The former displayed two carbonyl absorption bands at 1725 (ketone) and 1672 cm^{-1} (thiolester) and the latter spectrum showed the required molecular ion peak at 252.1184.

The cyclization of diketo thiolester **35** to the corresponding bridged compound **44** was found to be less facile. In benzene solution at ~4°C, the reaction was very slow. On the other hand, complex mixtures were produced when higher reaction temperatures were attempted. However, when the reaction was carried out in methylene chloride at 0°C for 1 h in the presence of magnesium sulfate to remove the water produced, a 53% yield (based on the consumed starting material) of the desired product **44** could be obtained along with a partial recovery of the starting material (33%). In the ir spectrum of the compound, the carbonyl absorptions were observed at 1756 and 1669 cm^{-1} characteristic of the five-membered ketone and the thiolester group respectively. The ^{1}Hmr spectrum displayed a broad singlet at δ 5.26 due to the vinylic proton, a methylene quartet ($J = 7$ Hz) at δ 2.88 and a methyl triplet ($J = 7$ Hz) at δ 1.25 due to the ethyl thiolester group, and a narrowly split doublet of doublets ($J = 2$, $J' = 1$ Hz) at δ 1.77 due to the vinylic methyl group. The molecular ion peak, which appeared at m/e 224.0868 in the mass spectrum, further confirmed the assigned structure.

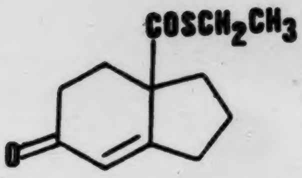
The cyclization of diketo thiolesters **36** and **37** proceeded readily under standard conditions to give the corresponding bridged compounds **45** and **46** in high yields. The spectral data of these compounds are as follows. In the mass spectra the molecular ions were observed respectively at m/e 238.1024 and 252.1186. In each ir spectrum, two strong carbonyl absorption bands were displayed, one at 1716 cm^{-1} (ketone) and the other at 1672 cm^{-1} (thiolester). The ^{1}Hmr spectra were also in support of the assigned structures. Compound **45** showed a multiplet at δ 5.65 for the vinyl proton and three methyl signals, two singlets at δ 2.28 (thiolester) and 1.04 (bridge-head methyl) and a doublet at δ 1.62 (vinylic methyl) with a long range coupling constant of 2 Hz. In addition to the multiplet at δ 5.65 for a vinylic proton, compound **46** also showed three methyl signals but in the form of two singlets (δ 2.28 and 1.09) and a triplet (δ 1.04) as expected.

The preparation of the bridged keto thiolesters **47** and **48** was also attempted but met with very little success. In both cases the required cyclization of the corresponding immediate precursors **34** and **38** proved to be difficult. Neither **34** nor **38** underwent the desired reaction under standard conditions with concentrated sulfuric acid. The lack of the desired reactivity of these compounds is in sharp contrast to the reactivity previously observed for the ketone analogues. A possible cause could be that, being secondary, the intermediate alcohol **49** is considerably more stable towards acids and thus more difficult to undergo dehydration required for the formation of the desired product. On the other hand, the aldol process is known to be reversible under acidic conditions and the alcohol could revert back to the thermodynamically more stable open form as shown in Scheme 2.

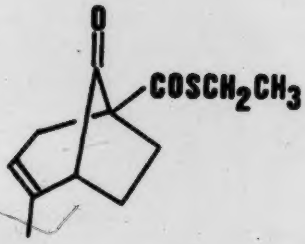

COSCH2CH3
O
R

39 R = H

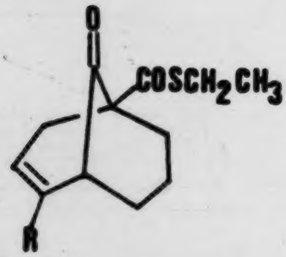
40 R = CH_3


COSCH2CH3
O

41

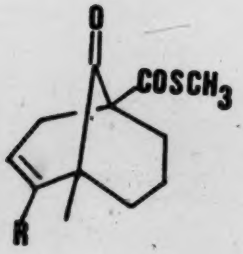

O
COSCH2CH3

44


O
COSCH2CH3
R

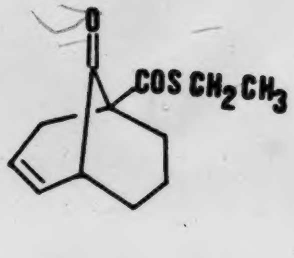
42 R = CH_3

43 R = CH_2CH_3

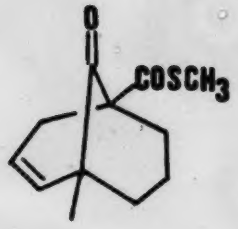


45 R = CH_3

46 R = CH_2CH_3

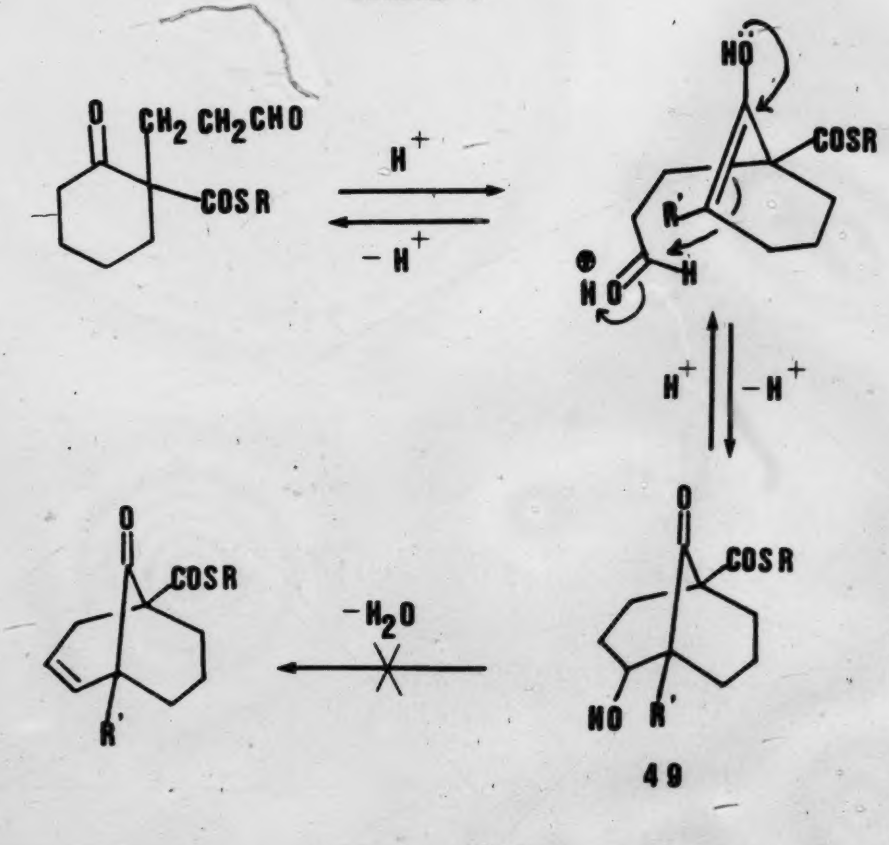


47



48

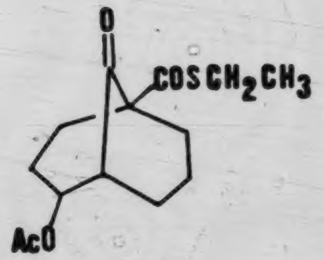
SCHEME 2



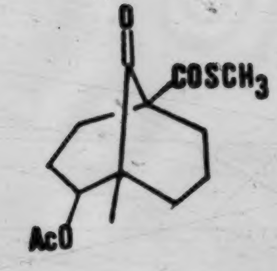
CH$_2$ CH$_2$CHO
COSR
H$^+$
− H$^+$
HO
COSR
R'
H
HO
H$^+$
−H$^+$
COSR
HO
R'
49
−H$_2$O
COSR
R'

In order to circumvent the difficulties encountered, the cyclizations of compounds **34** and **38** were attempted in the presence of acetic anhydride to trap the intermediate alcohols **49**. When the reaction was performed under acidic conditions (sulfuric acid), compound **34** was consumed rather rapidly (30 min) even at low temperature. However the product formed was shown to be not the desired acetate **50** but keto thiolester **29** resulting from a retro-Michael reaction. Similar results were obtained when keto aldehyde **34** was subjected to treatment with sodium hydride and acetic anhydride in refluxing 1,2-dimethoxyethane.

The cyclization of keto aldehyde **38** was also attempted with the assistance of acetic anhydride. The best results were obtained when the trapping agent, compound **38**, and potassium carbonate were stirred in acetone for 24 h. Under these conditions, a small amount (~20%) of a product was formed. This compound showed three carbonyl absorption bands at 1740, 1703, and 1670 cm^{-1} in the ir spectrum and three methyl singlets at δ 2.28, 2.26 and 0.91 in the ^{1}Hmr spectrum. On the basis of these spectral data, the desired structure **51** could be tentatively assigned to this compound. The low yield of its formation, however, makes the cyclization procedure synthetically unattractive.


O
COSCH2CH3
AcO

50


O
COSCH3
AcO

51

The results obtained for the aldol condensation reactions discussed in this section are further compiled in Table 2.

3. Some Synthetic Applications of the Annelation Products

The annelation process described above provides a viable alternative to the commonly used β-keto ester approach[46,48] to the construction of bridged and fused ring systems with concomitant introduction of a reactive functionalized substituent at the angular position. The thiolester group may be transformed to a number of other important functionalities, often under mild and specific conditions as discussed in the Introduction section, thus providing greater flexibility in the annelation reaction. A feature which is of obvious synthetic utility is the direct reduction of the thiolester to the alcohol[7,8] using Raney nickel without need of protection of the ketone carbonyl. This worked particularly well in the case of the bridged compounds. Thus, treatment of enone **42** with *ca.* ten-fold (by weight) excess of W-2 Ra-Ni in benzene for 30 min resulted in the formation of alcohol **52** in 88% yield. Alcohol **52** showed, in the ir spectrum, only one carbonyl absorption at 1711 cm^{-1}, along with a strong band

Table 2. Cyclization of the Michael adducts.

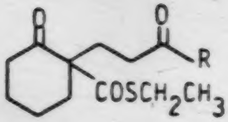
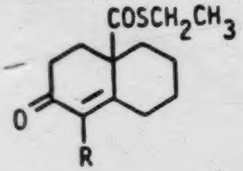
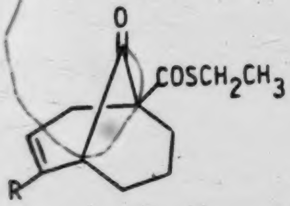
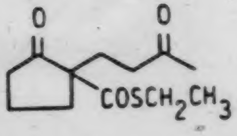
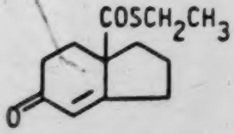
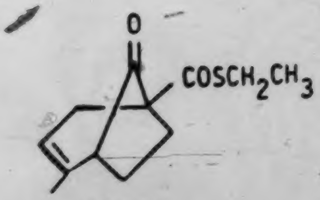
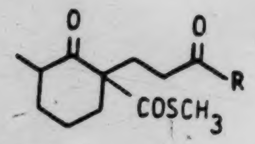
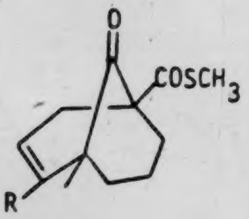
Michael adduct	Catalyst	Time(h)	Product	Yield(%)
 **32** R=CH_3 **33** R=CH_2CH_3				
	p-TsOH	10	**39** R=H	98
		19	**40** R=CH_3	100
				
	conc. H_2SO_4	$\frac{1}{2}$	**42** R=CH_3	93
		$\frac{1}{2}$	**43** R=CH_2CH_3	95
 **35**	p-TsOH	11	 **41**	90
	conc. H_2SO_4	1	 **44**	53

Table 2. Cyclization of the Michael adducts. (continued)

Michael adduct	Catalyst	Time(h)	Product	Yield (%)
				
36 R=CH_3	conc. H_2SO_4	$\frac{1}{2}$	**45** R=CH_3	100
37 R=CH_2CH_3		$1\frac{1}{6}$	**46** R=CH_2CH_3	81

at 3460 cm^{-1} for the newly formed hydroxy group and a carbon-carbon double bond absorption at 1675 cm^{-1}. In the ^{1}Hmr spectrum, the signals characteristic for an ethyl thiolester were absent and replaced by two doublets at δ 3.32 and 3.21, each with a large geminal coupling constant of 22 Hz, for the methylene protons adjacent to the hydroxyl group. The ^{1}Hmr spectrum also indicated the presence of a vinylic proton at δ 5.61 as a multiplet and a vinylic methyl group at δ 1.67 as a broad singlet, thus confirming that the carbon-carbon double bond was intact during the reduction. This was also evident from the mass spectrum which showed a molecular ion peak at m/e 180.1151 in agreement with the required molecular formula of $C_{11}H_{16}O_2$.

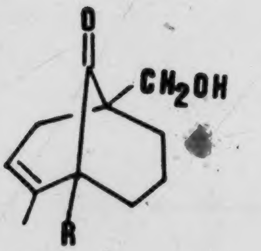
It is noteworthy that, although the thiolester group present in enone **42** is part of a β-keto thiolester system, it is also directly attached to a bridge-head carbon atom. As such, it is expected to behave in the same way as an ordinary thiolester group towards Raney nickel, since the stabilizing effect of the ketone on whatever the intermediate resulting immediately from the complete removal of the thiolester moiety, which apparently provides the driving force for the observed dealkylthiol-carbonylation reaction of normal β-keto thiolesters,[35,36,38] can not prevail.

Four additional cases were examined. The results were all comparable. Treatment of enone **45** with Ra-Ni in benzene for 30 min gave an 89% yield of keto alcohol **53.** Similarly, reduction of enones **46** and **44** furnished the corresponding keto alcohols **54** and **55** in 84% and 53% yields respectively. The only exception was the reduction of enone **43.** When the reduction was carried out with freshly prepared W-2 Raney nickel, a mixture of keto alcohol **56** and diol **57** was formed in ca. 7:2 ratio and in a total yield of 85%. The formation of the latter compound was apparently due to the highly reactive Ra-Ni used which also effected the reduction of the ketone carbonyl.

The structural assignments of the above compounds follow clearly from their spectral data. In addition to the required molecular ion peak in the mass spectrum, each of the keto alcohols **53, 54,** and **56** showed, in the ^{1}Hmr spectrum, a multiplet centered at ~δ 5.6 for a vinylic proton and a pair of mutually coupled doublets (22 Hz in all cases) in the region of ~δ 3.3 for the methylene protons neighboring the hydroxy group. Furthermore, a carbonyl absorption and a hydroxy band were observed, typically at ~1700 and 3500 cm^{-1} respectively, in each of the ir spectra. The carbonyl absorption of keto alcohol **55** appeared at 1742 cm^{-1} in the ir spectrum as expected due to the presence of a cyclopentanone system. In contrast to those of the bicyclo[3.3.1]nonane analogs, the ^{1}Hmr spectrum of this compound was found to be also quite unique. Its hydroxy-bearing methylene group appeared as a broad singlet at δ 3.50. As well, the vinylic proton was observed at a much higher field of δ 5.19. Diol **57** showed a strong hydroxy band at 3380 cm^{-1} and the complete absence of carbonyl absorption in the ir spectrum. In the ^{1}Hmr spectrum, two doublets were observed, one at δ 3.85 with a coupling constant of 4 Hz for a single proton and the other at δ 3.43 with a coupling constant of 3 Hz for two protons. These signals were readily ascribed to the protons adjacent to the hydroxyl groups. Also in agreement with the structural assignment were a multiplet observed for the vinylic proton at δ 5.38 and a methyl triplet (J = 8 Hz) at δ 0.98. Diol **57** appears to be a single stereoisomer. Its stereochemistry, however, remains to be determined.

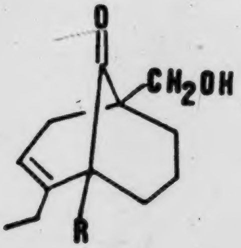
The results obtained from the reduction of the bridged enones **42**, **43**, **44**, **45**, and **46** are further compiled in Table 3.

The Raney nickel reduction of the fused system was also examined. On exposure to Ra-Ni, fused compounds, such as **39**, possessing a vinylogous β-keto thiolester, are expected to result either in the complete removal of the



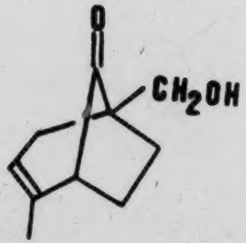
52 R = H

53 R = CH_3

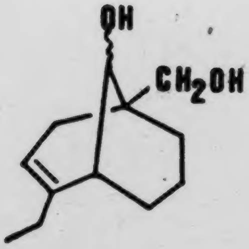


54 R = CH_3

56 R = H

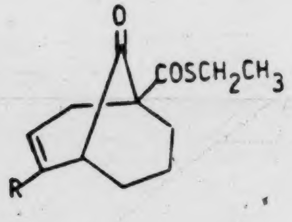
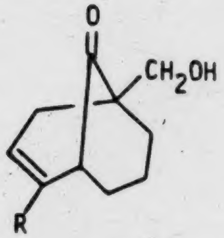
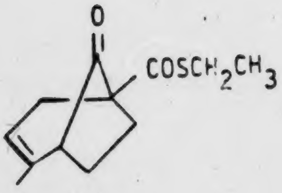
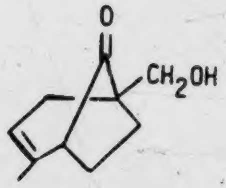
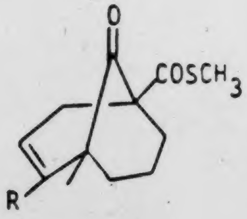
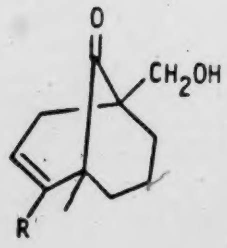


55



57

Table 3. Raney-nickel reduction of the bridged enones.

Enone	Time(h)	Product	Yield(%)
			
42 R=CH_3	$\frac{1}{2}$	**52** R=CH_3	88
43 R=CH_2CH_3	$\frac{1}{4}$	**56** R=CH_2CH_3	66
			
44	$\frac{1}{3}$	**55**	53
			
45 R=CH_3	$\frac{1}{2}$	**53** R=CH_3	89
46 R=CH_2CH_3	$\frac{1}{2}$	**54** R=CH_2CH_3	84

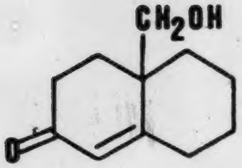
thiolester group analogous to those observed for β-keto thiolesters[38,44] or in the reduction of the thiolester group to the alcohol level in parallel to the observed reduction of ordinary thiolesters. Unfortunately, these two different modes of reactivity were found to be highly competitive. Invariably, a rather complex mixture consisting, among others, both the elimination and the reduction products (in various ratios) was formed regardless of the grade of the Ra-Ni applied and only modest yields of these two types of compounds could be obtained. For example, the reduction of enone **39** gave only a 45% yield of the corresponding enone alcohol **58** under carefully controlled conditions using deactivated (refluxing acetone; 20 min) Raney nickel. Thus, the direct conversion of the fused annelation products to the corresponding keto alcohols or compounds resulting from dealkylthiocarbonylation can not be considered as general or highly synthetically useful.

A more fruitful area of synthetic application is illustrated in the following examples, which show that the removal of the ketone carbonyl of a fused annelation product and the reduction of the angular substituent to the alcohol level can be simultaneously effected via a thioketal derivative. Treatment of enone **39** with 1,2-ethanedithiol in methylene chloride in the presence of a catalytic amount of boron trifluoride etherate gave an 89% yield of the corresponding thioketal **59**, which showed absorption bands at 1683 and 1674 cm^{-1} in the ir spectrum due to the thiolester group and the carbon-carbon double bond respectively. The ^{1}Hmr spectrum confirmed the presence of the thioketal group by displaying a four-proton multiplet in the δ 3.24 region. In addition, a broad singlet at δ 5.78 for the vinylic proton, and characteristic signals for the ethyl thiolester group, consisting of a triplet at δ 1.22 and a quartet at δ 2.81, were also observed. The molecular formula of $C_{15}H_{22}O_3$ was verified by the mass spectrum showing a molecular ion peak at m/e 319.0839.

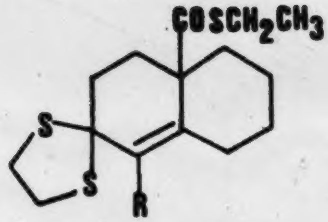
The reduction of thioketal **59** with Raney nickel in benzene at room temperature for 2 h gave the white crystalline alcohol **60**, m.p. 66-67°C, in 82% yield, as a result of concomitant desulfurization of both the thioketal and the thiolester groups. The vinylic proton appeared in the ^{1}Hmr spectrum at δ 5.50 as a broad triplet with a coupling constant of 4 Hz. The two-proton singlet at δ 3.60 and another singlet at δ 2.49 for one hydrogen atom were readily assigned to the hydroxymethylene group. In the ir spectrum, two diagnostic absorption bands were observed at 3478 and 1658 cm^{-1} due to the hydroxy group and the carbon-carbon double bond respectively. The elemental analysis and the mass spectrum, which showed a parent ion at m/e 166.1360, further substantiated the assigned structure of **60**.

Under similar conditions, thioketalization of enone **40** furnished, in 88% yield, thioketal **61** which was readily reduced with Ra-Ni to give a 74% yield of alcohol **62** as a white solid, m.p. 69-70°C. The former compound showed a parent ion at m/e 328.0987 in the mass spectrum, a strong carbonyl absorption at 1682 cm^{-1} in the ir spectrum, and a four-proton multiplet at δ 3.28 characteristic for the thioketal group in the ^{1}Hmr spectrum. In the ir spectrum of the latter compound **62**, the carbonyl absorption was absent while the hydroxy group gave a characteristic band at 3360 cm^{-1}. The ^{1}Hmr spectrum displayed a methyl singlet at δ 1.59 and a methylene singlet at δ 3.49 due to the angular substituent. The molecular ion peak at m/e 180.1150 displayed by the mass spectrum served as a further confirmation of the structure.

As a further example to demonstrate the generality of the above synthetic application, enone **41** possessing a bicyclo[4.3.0]nonane system was subjected to thioketalization. Subsequent treatment of thioketal **63**, obtained in quantitative yield, with Raney nickel resulted in the formation of alcohol **64** in 88% yield. The ir and ^{1}Hmr spectrum of compounds **63** and **64** were found to be

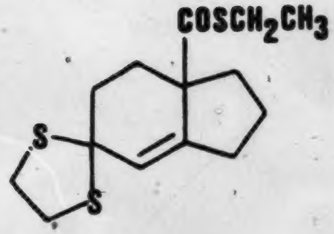


58

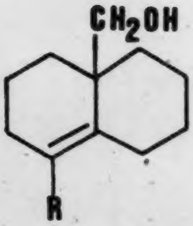


59 R = H

61 R = CH$_3$

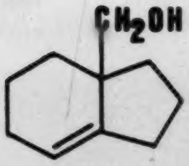


63



60 R = H

62 R = CH$_3$



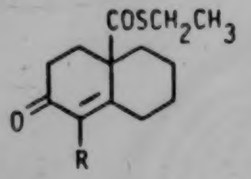
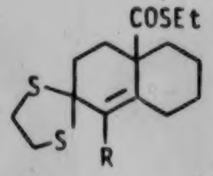
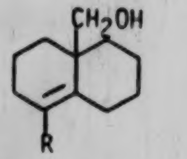
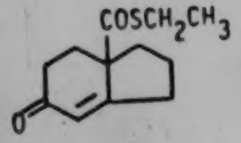
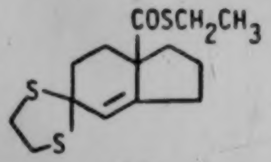
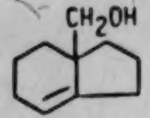
64

similar to those of the corresponding bicyclo[4.4.0]decane homologs **59** and **60**, while the mass spectra showed, in each case, a reduction of 14 mass units as required.

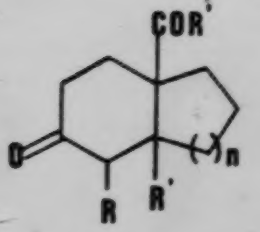
The transformation of enones **39**, **40**, and **41** to the corresponding alcohols **60**, **62**, and **64** are further outlined in Table 4.

The conjugate addition of organocopper reagents to α,β-unsaturated carbonyl compounds is a well-established synthetic process.[49] It is also known that thiolesters undergo reactions with organocopper reagents to give ketones.[34] Thus, the fused keto thiolesters (e.g. **39**) were expected to react with lithium diorganocuprates to give compounds of type **65** as a result of the simultaneous occurrence of the above reactions. This type of transformation is of considerable synthetic potential as it allows the establishment of two consecutive quaternary carbon centers along with the incorporation of a highly versatile functionality into the molecule. It was with this realization, that we examined the reaction of **39** with lithium dimethylcuprate (4 mol equiv.) in ether at -40°C. Contrary to the expectation, a crystalline carboxylic acid, m.p. 88-88.5°C, was formed persistently in spite of the extreme care undertaken to exclude moisture. The acid, which was produced to the extent of 78% yield, was later shown to possess the structure of **66** by the

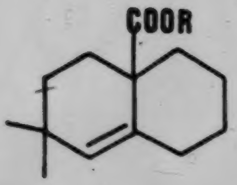
Table 4. Thioketalization of enones and reduction of thioketal with Raney-nickel.

Enone	Catalyst	Time(h)	Thioketal	Yield	Time(h)	Product	Yield (%)
 **39** R=H **40** R=CH_3	$BF_3 \cdot Et_2O$ $BF_3 \cdot Et_2O$	18 20	 **59** R=H **61** R=CH_3	89 88	2 $1\frac{2}{3}$	 **60** R=H **62** R=CH_3	82 74
 **41**	$BF_3 \cdot Et_2O$	22	 **63**	100	$\frac{2}{3}$	 **64**	88

following spectral data. The carboxyl group was clearly defined by the appearance of two characteristic bands at 3400-2400 and 1700 cm^{-1} in the ir spectrum. The ^{1}Hmr spectrum showed a singlet at δ 12.18 for one proton, confirming the presence of a carboxyl group, as well as a singlet at δ 5.19 for an uncoupled vinylic proton, suggesting that the double bond was intact. In addition, two sharp singlets, integrating to three protons each, were observed at δ 0.97 and 0.91. These signals were readily ascribed to methyl groups. The mass spectrum, which displayed a molecular ion peak at m/e 208.1463, further revealed the molecular composition of $C_{13}H_{20}O_2$ in agreement with the assigned structure. The assignment was further confirmed as follows. Esterification of acid **66** with methyl iodide and potassium carbonate in refluxing acetone gave rise to the corresponding methyl ester **67** identical with an authentic sample prepared from dimedone (**68**) according to the sequence outlined in Scheme 3. Dimedone (**68**) was treated with ethanol in benzene in the presence of p-toluenesulfonic acid with a Dean-Stark water separator. Reduction of the resulting ethoxy enone with lithium aluminum hydride in ether followed by acidic workup gave enone **69** which was subjected to hydrogenation using 5% palladium on barium carbonate as a catalyst.[50]



65

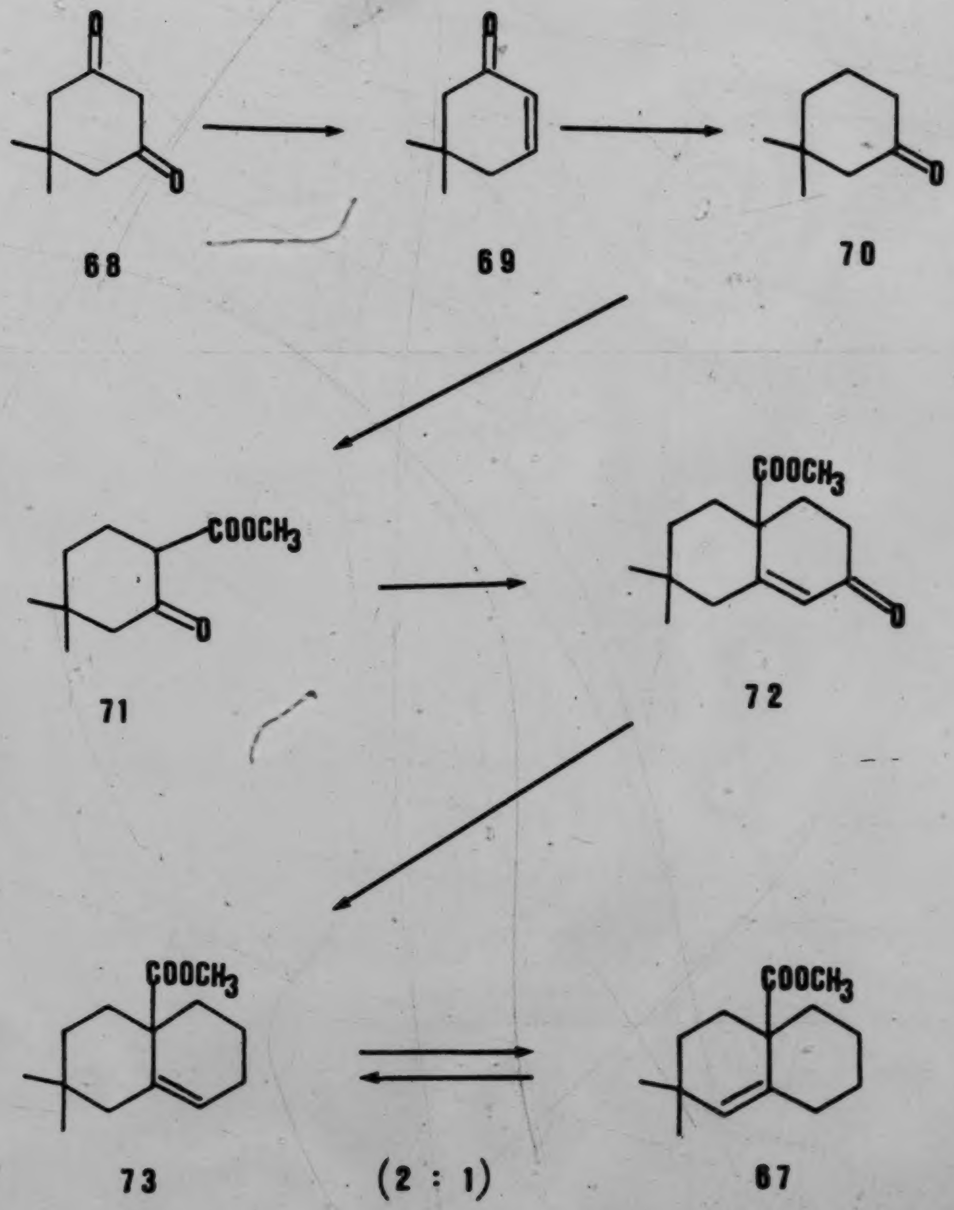


66 R = H

67 R = CH_3

Carbomethoxylation of 3,3-dimethylcyclohexanone **70** thus obtained with sodium hydride and dimethyl carbonate in refluxing 1,2-dimethoxyethane gave mainly keto ester **71** along with a small amount of the regioisomer.[51] Michael addition of **71** to methyl vinyl ketone using DABCO as a base followed by an intramolecular aldol condensation catalyzed by p-toluenesulfonic acid led to the formation of enone ester **72**. This compound was subjected to thioketalization with 1,2-ethanedithiol and boron trifluoride etherate in methylene chloride. Subsequent desulfurization with Raney nickel afforded ester **73**. The ir and mass spectra of this compound were found to bear close resemblance to those of ester **67**. Their ^{1}Hmr spectra were however markedly different. The ^{1}Hmr spectrum of **67** showed a sharp singlet for the vinylic proton at δ 5.18 and three methyl singlets at δ 3.61, 0.94, and 0.91. In the case of compound **73**, three methyl singlets appeared at δ 3.68, 0.90, and 0.80, while the signal due to the vinylic proton was observed as a broad singlet at δ 5.53. Compounds **73** and **67** were correlated by isomerization as follows. Treatment of compound **73** with p-toluenesulfonic acid in refluxing benzene for 12 h resulted in the formation, in quantitative yield, of a mixture consisting of two parts of the starting ester **73** and one part of an isomeric compound which was found to be

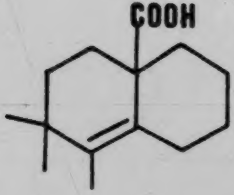
SCHEME 3


68
69
70
COOCH3
71
COOCH3
72
COOCH3
73
(2 : 1)
COOCH3
67

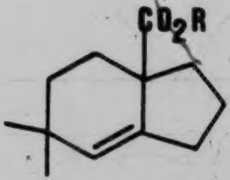
identical with ester **67**. The same equilibrium mixture was also obtained, when ester **67** was treated with p-toluenesulfonic acid under similar conditions. Thus, the structure of carboxylic acid **66** was firmly established.

The direct conversion of a ketone carbonyl into a gem-dimethyl group by the action of lithium dimethylcuprate is, to the best of our knowledge, unprecedented. This transformation appears to be general for compounds structurally related to enone **39**. Consistent results were obtained for enones **40** and **41**. Treatment of the former compound with lithium dimethylcuprate under conditions similar to those described previously for enone **39** gave rise to acid **74**, m.p. 105-106°C, in 94% yield. The reaction of compound **41** and lithium dimethylcuprate was found to be equally facile giving rise to a 61% yield of **75**, m.p. 92.5-93.5°C. The structure of **75** was further confirmed by esterification with methyl iodide and potassium carbonate in acetone to give the corresponding methyl ester **76**.

It is worth noting that the above results obtained for the vinylogous β-keto thiolesters are in sharp contrast to the result obtained for the O-ester analog **77** which, on similar treatment with lithium dimethylcuprate, gave rise to a 1:3 mixture of two epimeric alcohols **78** and **79** in a total yield of 68%. Compound **77** was also found to



74



75 $R = H$

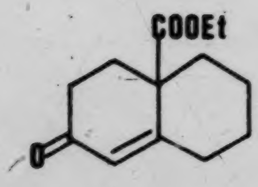
76 $R = CH_3$

react similarly with methyllithium to give, in 97% yield, alcohols **78** and **79** but, interestingly, in a reversed ratio of ca. 3.5:1. The stereochemistry of these alcohols follows from the following observations. Although both compounds were recovered intact after treatment with sodium hydride in 1,2-dimethoxyethane at room temperature, at reflux, alcohol **78** was transformed to diene **80** while its epimer **79** remained unchanged. Compound **80** was apparently produced via the lactone intermediate **81** followed by the extrusion of carbon dioxide involving a retro-Diels-Alder reaction. As required by the formation of **80**, the stereochemistry of the starting alcohol was assigned as shown in formula **78**.

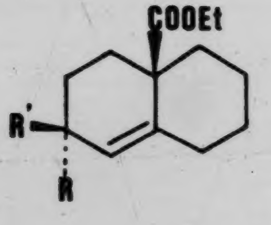
Mechanistically, the unusual replacement of a ketone carbonyl with a gem-dimethyl may be rationalized by invoking a lactone intermediate such as **81** which could be produced by stereoselective addition of lithium dimethylcuprate to enone **39** in a 1,2-fashion (**39**→**82**) followed by lactonization (**82**→**81**). Further coupling of lactone **81** with lithium dimethylcuprate could lead to the observed product **66**. In order to determine the validity of this mechanistic rationale, the preparation of lactone **81** was sought. As indicated above, this compound **81**, due to its thermal instability, could not be effectively prepared by lactonization of alcohol **78** which required rather severe reaction conditions.

To facilitate the lactonization, the thiolester analog of compound **78** was prepared from enone **39** which was subjected to treatment with methyllithium in ether at -78°C for 15 min. The reaction proceeded with complete stereoselectivity giving rise to alcohol **82** as the sole product in 88% yield. The ^{1}Hmr spectrum of this compound displayed a one-proton singlet at δ 5.58 due to the vinylic proton and a methyl singlet at δ 1.08. The quartet and the triplet characteristic for the ethyl thiolester group appeared at δ 2.81 and 1.24 respectively. In the ir spectrum, the diagnostic absorption bands were observed for the hydroxy group (3460 cm^{-1}) and the thiolester carbonyl (1680 cm^{-1}). The structure was further substantiated by the mass spectrum which exhibited a prominent peak at m/e 239.1105 which was attributed to the loss of a CH_3 unit. The stereochemistry of the compound, however, could not be unambiguously determined at this point on the basis of the spectral data. The fact that it possesses the desired stereochemistry as depicted follows from the subsequent lactonization.

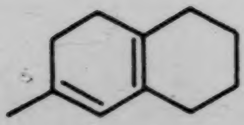
On exposure to sodium hydride in 1,2-dimethoxyethane at room temperature, alcohol **82** underwent cyclization to give the desired lactone **81** along with a small amount of



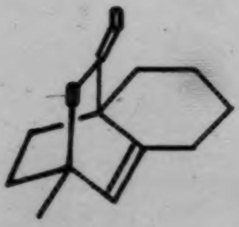
77



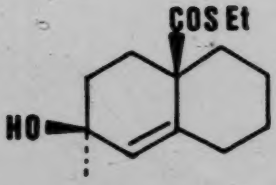
78 R = CH_3
R' = OH
79 R = OH
R' = CH_3



80



81



82

diene **80** resulting from the decomposition of **81**. The presence of diene **80** was indicated by direct comparison with an authentic sample obtained previously by thin-layer chromatography. It was further confirmed by comparison of the ^{1}Hmr spectrum of pure **80** with that of the mixture which showed two sets of signals; the minor set of signals was found to be identical with those of diene **80**. The major set of signals, consisting of two singlets, one at δ 5.78 for the vinylic proton and the other at δ 1.74 for the angular methyl group, could be attributed to lactone **81**. In agreement with this assignment, the ir spectrum of the mixture showed a diagnostic δ-lactone absorption at 1750 cm^{-1}. Although the mass spectrum failed to give the parent ion peak, the appearance of two fragments at m/e 164.1199 and 148.1233, due to the loss of CO and CO_2 respectively, lent further support to the structural assignment. By integration of the ^{1}Hmr spectrum, the ratio of diene **80** and lactone **81**, which were obtained in a total yield of 100%, was determined to be approximately 1:3. The separation of these two compounds proved to be difficult. Several attempts made to remove diene **80** by distillation and column chromatography resulted in invariably the decomposition of the desired lactone **81** to diene **80**. Consequently, the mixture was used for the subsequent coupling reaction without purification.

When the ca. 1:3 mixture of **80** and **81** was treated with lithium dimethylcuprate (2 mol equiv.) in ether at -40°C, a single product was formed rapidly at the expense of lactone **81**. The compound, thus obtained in ca. 85% yield based on lactone **81**, was found to be identical in all respects with acid **66**, previously obtained directly from the reaction of enone **39** and lithium dimethylcuprate. These results are in agreement with the mechanistic pathway proposed for the latter unusual reaction.

In conjunction with the easy accessibility of the required precursors, the unique and efficient transformation of the carbonyl group to a gem-dimethyl described above should have broad synthetic application, particularly in the area of pentacyclic triterpenoids, many of which have D/E ring systems similar to that of **66**.[52]

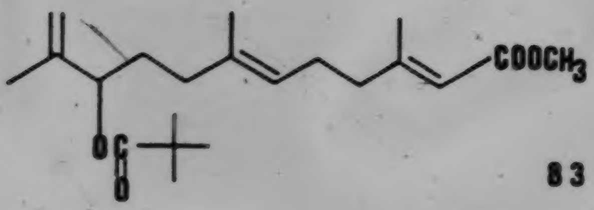
4. Coupling of Allylic Pivalates with Lithium and Magnesium Organocopper Reagents.

As described in the preceding section, lactone **81** coupled remarkably effectively with lithium dimethylcuprate under extremely mild conditions to give acid **66**, in spite of the steric congestion at the site of reaction. An extrapolation of these findings suggested that allylic pivalates might possess interesting properties in coupling with organocuprates.*

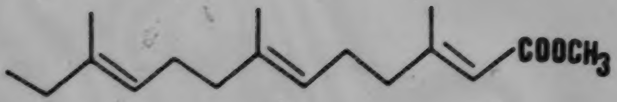
In accordance with our expectations, allylic pivalates were found to react smoothly with lithium diorganocuprates as well as with RMgX-CuI (2:1) complexes under mild conditions giving rise to coupling products in high yields. In a typical experiment involving lithium diorganocuprate, a solution of alkyllithium (6 mmol) was added with stirring to a suspension of freshly recrystallized cuprous iodide (3.6 mmol) in ether (20 mL) at 0°C under an argon atmosphere. After 10 min, the mixture was chilled to -40°C and a solution of the allylic pivalate (1 mmol) in ether (5 mL) was introduced. The reaction was monitored by thin-layer chromatography. Upon completion (1-4 h), the reaction mixture was acidified with 1 N aqueous hydrochloric acid and extracted with ether. Work-up of the extracts in the usual manner gave the crude product which was purified by column chromatography on silica gel and/or by Kugelrohr distillation. With the magnesium cuprates, the reactions

---

* In an isolated case,[53] allylic pivalate **83** was shown to couple with lithium dimethylcuprate giving triene ester **84** as the major product.



83



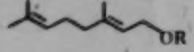
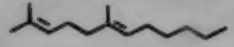
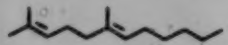
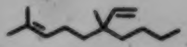
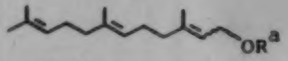
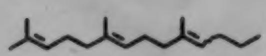
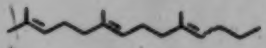
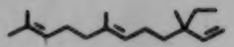
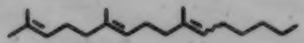
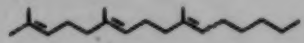
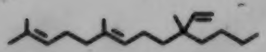
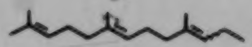
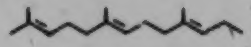
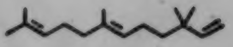
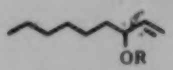
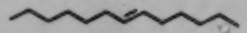
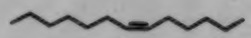
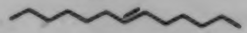
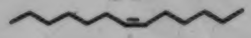
84

were carried out in a similar fashion except that a molar ratio of 6:3:1 was used for alkylmagnesium halide (in place of alkyllithium), cuprous iodide and the reactant and the reaction temperature was maintained at 0°C throughout. Several reactions attempted at -40°C failed and the use of smaller amounts of the reagents was shown experimentally to be substantially less effective.

Table 5 summarizes the results obtained. The allylic pivalates examined included both the primary and the secondary ones with the double bond substituted in various patterns. These pivalates were readily prepared from the corresponding alcohols by esterification with pivaloyl chloride (1.5 equiv.) and pyridine (1.2 equiv.) in ether at room temperature. We have also attempted to examine the 3° allylic pivalates but have not been able to make these substrates effectively due to their instability; numerous attempts to esterify 3-methyl-4-cholesten-3-ol and _trans_-2-methyl-3-decen-2-ol resulted consistently in the formation of the dehydration products in major quantities. The structures and ratios (where applicable) of products were determined by spectroscopic and/or chemical methods as detailed below.

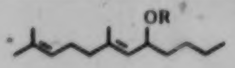
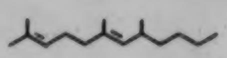
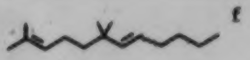
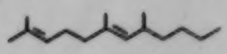
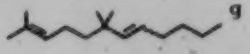
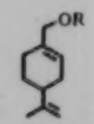
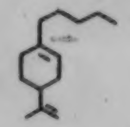
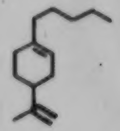
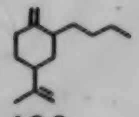
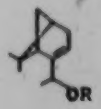
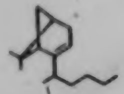
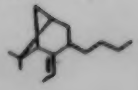
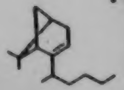
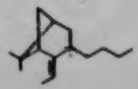
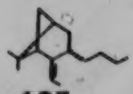
The diene **86**, obtained from geranyl pivalate (**85**) (Entry 1) as the sole product in 100% yield, showed a parent ion at m/e 194.2031 in the mass spectrum and a weak

Table 5. Coupling of allylic pivalates with lithium and magnesium organocopper reagents.

Entry	Allylic Pivalate R = COC(CH$_3$)$_3$	Reagents	Time^b (h)	Product(s) (ratio^e)	% Yield
1	 **85**	*n*-BuLi/CuI	2		100
2		*n*-BuMgBr/CuI	1	 **86** +  **87** (1:3)	95
3	^{a} **88**	EtLi/CuI	2	^{a}	95
4		EtMgBr/CuI	1.5	^{f} **89** +  **90** (1:4)	100
5		*n*-BuLi/CuI	2	^{a}	100
6		*n*-BuMgBr/CuI	1	^{f} **91** +  **92** (1:6)	99
7		MeLi/CuI	2^c	^{a}	90
8		MeMgI/CuI	8.5^d	^{f} **93** +  **94** (1:6)	65
9	 **95**	*n*-BuLi/CuI	1	 **96** +  **97** (6:1)	92
10		*n*-BuMgBr/CuI	1	 +  (2:1)	92

continued.....

Table 5. Coupling of allylic pivalates with lithium and magnesium organocopper reagents. (continued)

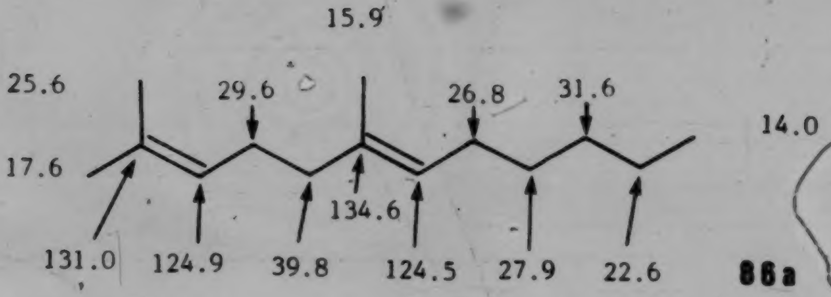
Entry	Allylic Pivalate R = COC(CH$_3$)$_3$	Reagents	Time[b] (h)	Product(s) (ratio[e])		% Yield
11		MeLi/CuI	4	 + [f]	(7:1)	62
12	98	MeMgI/CuI	3	 + [g] 99 100	(1:6)	97
13		n-BuLi/CuI	2	 102		92
14	101	n-BuMgBr/CuI	1	 +  103	(1:11)	73
15	 104	n-BuLi/CuI	2	 +  105 106		81
16		n-BuMgBr/CuI	1.5	 +  +  107	(1:7.5:5)	86

---

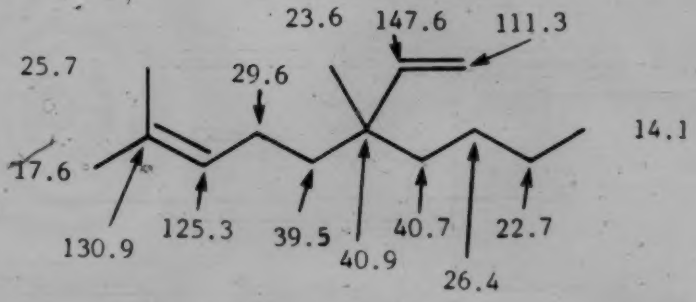
[a] E:Z ≅ 2.5:1. [b] Unless otherwise stated, reactions were carried out according to the general procedures described in the text. [c] This reaction was performed at -20°C. [d] This reaction was performed at room temperature. [e] The ratios of products were determined by nmr (^{1}H and ^{13}C) and/or gc analyses. [f] The ratio of the two geometric isomers could not be determined with reasonable accuracy. [g] E:Z ≅ 15:1.

carbon-carbon absorption band at 1664 cm^{-1} in the ir spectrum. The ^{1}Hmr spectrum exhibited a multiplet at δ 5.12, integrating to two hydrogen atoms due to the vinylic protons, two methyl singlets at δ 1.60 (six protons) and δ 1.70, and a methyl triplet at δ 0.91 with a coupling constant of 7 Hz. The mixture (95% yield) resulted from pivalate **85** and the n-BuMgBr-CuI (2:1) reagent (Entry 2), along with a small amount of geraniol (5% yield), showed two sets of signals in a ratio of 1:3 in the ^{1}Hmr spectrum. The minor signals were found to coincide with those of diene **86**. The major set of signals, which was attributed to diene **87**, included three doublets of doublets at δ 5.69 (J = 17, J' = 11 Hz), 4.96 (J = 11, J' = 2 Hz) and 4.88 (J = 17, J' = 2 Hz), characteristic for a vinyl group attached to a quaternary carbon. The remaining vinyl proton appeared at δ 5.11 as a multiplet. In addition, a methyl triplet (J = 7 Hz) at δ 0.88 and three methyl singlets at δ 1.68, 1.58 and 0.94 were displayed. In agreement with the structural assignments, the ^{13}Cmr spectrum also showed two sets of signals in ca. 1:3 ratio. These signals were assigned as outlined in formulas **86a** and **87a**.

Farnesyl pivalate (**88**) was subjected to coupling with a large number of organocopper reagents. The structures of products **89-94** and the compositions of products in the


15.9
25.6
29.6
26.8
31.6
14.0
17.6
134.6
131.0
124.9
39.8
124.5
27.9
22.6

86a


23.6
147.6
111.3
25.7
29.6
14.1
17.6
130.9
125.3
39.5
40.9
40.7
26.4
22.7

87a

case of mixtures were deduced mainly by careful examination of the ^{1}Hmr spectra in the same manner as described above for dienes **86** and **87**. Suffice it to say that the starting farnesol used was a mixture of two stereoisomers due to the double bond bearing the hydroxymethylene group (E:Z = 2.5:1). It appears that this stereoisomerism was inherited by the relevant products **89**, **91**, and **93**. It is also noteworthy that the reactions of **88** with both the lithium and magnesium methylcopper reagents (Entries 7 and 8) proceeded more effectively at temperatures about 20°C higher than the standard ones. At these temperatures, the formation of farnesol as a by-product was shown to be minimal. Table 6 summarizes the results obtained for the reaction of **88** and lithium dimethylcuprate at various temperatures.

The coupling of pivalate **95** with butylcopper reagents gave rise to trans- (**96**) and cis-6-tridecene (**97**). With the lithium reagent (Entry 9), the trans to cis ratio was found to be 6:1, while the magnesium reagent gave rise to **96** and **97** in a 2:1 ratio. The ^{1}Hmr spectra of the mixtures, which showed, in each case, a poorly resolved two-proton multiplet at δ 5.38 for the vinylic protons and two methyl triplets (J = 6 Hz each) at δ 0.90 and 0.89, were not sufficiently informative for assigning the stereochemistry and determining the composition of the

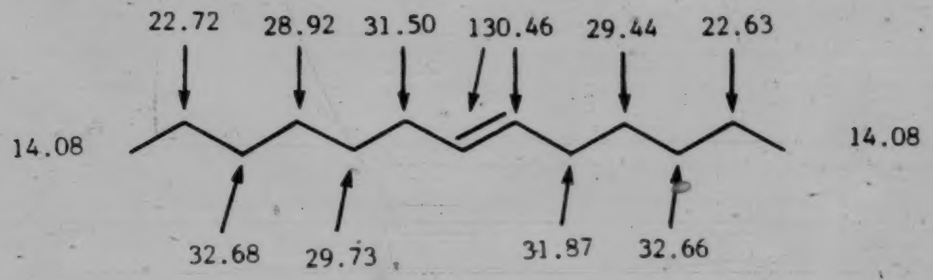
Table 6. Coupling of farnesyl pivalate **88** with lithium dimethylcuprate at various temperatures.

Temperature(°C)	Time(h)	Product **93**	Farnesol	Pivalate **88** Recovered
0	2	72%	28%	—
-22	2	80%	9%	11%
-40	2	66%	27%	7%
-78	11	31%	22%	47%

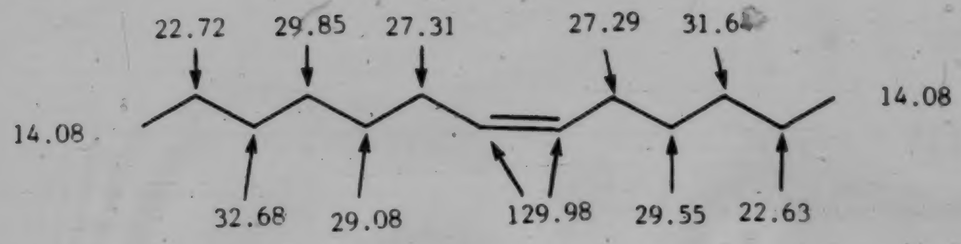
mixtures. These determinations were made on the basis of the ^{13}Cmr spectra. With the assistance of trans- and cis-4-octene as well as trans- and cis-3-octene[53] as model compounds, the ^{13}Cmr signals were assigned as shown in formulas **96a** and **96b** and the stereochemistry and the ratio, in each mixture, of the two compounds were tentatively deduced.

Pivalate **98** reacted with lithium dimethylcuprate to give a 7:1 mixture of the isomeric dienes **99** and **100**. These two compounds were also produced using the MeMgI-CuI (2:1) reagent but in a significantly different ratio of 1:6 with the latter isomer predominating. The ratios of the products were determined by ^{1}Hmr analysis. In the ^{1}Hmr spectra, the vinylic protons of both isomers appeared at δ 5.10 as a multiplet and the C-7 proton of compound **99** at δ 4.88 as a doublet, whereas the C-7 and C-8 protons of compound **100** were found in the δ 5.3 region. Integration of these signals led to the estimated ratios of the products.

The coupling reaction of (±)-perillyl pivalate (**101**) and lithium di-n-butylcuprate (Entry 13) afforded diene **102** as the sole product. The structure was readily evident from the ^{1}Hmr spectrum which indicated the presence of three vinylic protons, two of which appeared as a singlet at δ 4.73 and the other as a multiplet at


22.72
28.92
31.50
130.46
29.44
22.63
14.08
14.08
32.68
29.73
31.87
32.66

96a

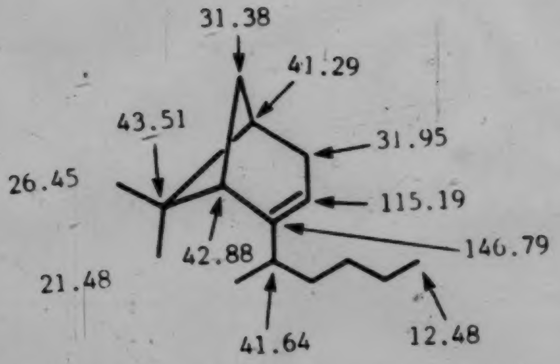

22.72
29.85
27.31
27.29
31.64
14.08
14.08
32.68
29.08
129.98
29.55
22.63

97a

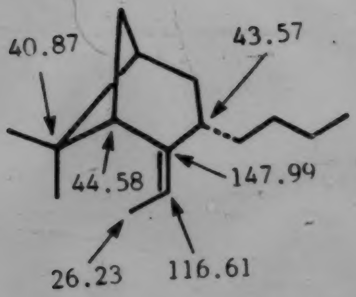
δ 5.41. With the magnesium reagent (Entry 14), diene **103** was found as the major product along with a small quantity of the isomer **102**. The former compound showed, in the ^{1}Hmr spectrum of the mixture, a narrowly split (1.2 Hz) triplet at δ 5.68 due to the vinylic protons of the isopropenyl moiety. Two other narrowly split triplets (J = 1.6 Hz each), integrating to one proton each, were also observed in the low field at δ 5.64 and 5.60. These signals were readily ascribed to the exocyclic methylene group. Compound **103** was further shown to be a mixture of two stereoisomers by the ^{13}Cmr spectrum of the mixture of **102** and **103** which displayed, apart from a set of signals corresponding to compound **102**, a major set of signals, apparently due to **103**.

A 2.2:1 mixture of structurally isomeric compounds **105** and **106** were produced by the coupling reaction of pivalate **104** and lithium di-n-butylcuprate. When the corresponding magnesium reagent was used, stereoisomers **106** and **107** were isolated in a 1.5:1 ratio together with a small amount of compound **105** (less than 8% of the total mixture). The tentative structural assignments of these compounds could be reached by a careful analysis of the ^{1}Hmr spectra which revealed the signals corresponding to each of these compounds. For **105**, a multiplet at δ 5.15 for the vinylic proton, a methyl doublet (J = 8 Hz) at δ 0.89, and a methyl triplet (J = 8 Hz) at δ 0.88 were observed. Isomer **106** displayed a quartet at δ 5.22 with a coupling constant of 7 Hz due to the vinylic proton, a triplet (J = 6 Hz) at δ 2.81 for the C-1 proton, and a vinylic methyl doublet at δ 1.50 with a 7 Hz coupling constant. These signals were also observed for compound **107** but at markedly different chemical shifts respectively at δ 4.99 as a doublet of quartets (J = 7, J' = 2 Hz), δ 2.42 as a broad triplet (J = 6 Hz), and δ 1.58 as a doublet of doublets (J = 7, J' = 2 Hz). Compounds **106** and **107** proved to be stereoisomers due to the double-bond rather than the chiral center bearing the *n*-butyl group by the following experiments.

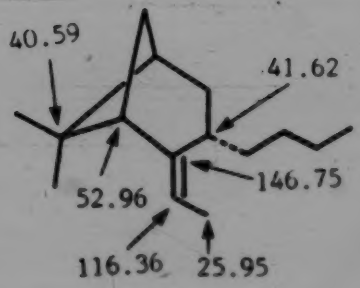
Ozonolysis of the mixture obtained from the magnesium *n*-butylcopper reagent followed by reductive work-up with dimethylsulfide gave ketone **108** as a major product in 88% yield. The compound showed a molecular ion peak at m/e 194.1662 in the mass spectrum and a strong carbonyl absorption at 1703 cm^{-1} in the ir spectrum. In the ^{1}Hmr spectrum, the C-1 proton appeared as a doublet (J = 6 Hz) at δ 2.59 and the C-3 proton as a multiplet at δ 2.52. A single triplet at δ 0.92 and two sharp singlets at δ 1.33 and 0.88 were also displayed for a total of three methyl groups indicating the presence of a single stereoisomer. The isolation of a single isomer of **108** in high yield strongly suggested that compounds **106** and **107** were double bond isomers. Furthermore, treatment of ketone **108** with 1 N aqueous sodium hydroxide in refluxing methanol for 16 h resulted in the epimerization of its enolizable α-carbon giving, in quantitative yield, an equilibrium mixture with the newly formed epimer predominating to the extent of 80%. The ^{1}Hmr spectrum of the mixture exhibited, in addition to signals due to the starting ketone **108**, a major set of signals consisting of a doublet ($J = 6$ Hz) at δ 2.59 (C-1 proton), a multiplet at δ 2.48 (C-3 proton), a methyl triplet at δ 0.93 and two singlets at δ 1.30 and 0.73 for the gem-dimethyl group. Since this new epimer was formed in major quantity under thermodynamically controlled conditions, its stereochemistry could be logically assigned as depicted in formula **109** in which the bulky n-butyl group is remote from the methyl group on the bridge carbon. Consequently, the stereochemistry of ketone **108** and the configuration of the chiral carbon of its precursors **106** and **107** were deduced as shown. The double bond stereochemistry of **106** and **107** were assigned on the basis of the ^{13}Cmr spectrum of the mixture obtained directly from the reaction of pivalate **104** and n-BuMgBr-CuI. Using α- and β-pinene as model compounds,[53] the ^{13}Cmr signals were assigned to compounds **105**, **106** and **107** as shown in formulas **105a**, **106a**


31.38
41.29
43.51
31.95
26.45
115.19
146.79
42.88
21.48
41.64
12.48

105a


40.87
43.57
44.58
147.99
26.23
116.61

106a


40.59
41.62
52.96
146.75
116.36
25.95

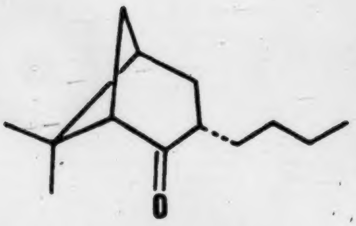
107a

and **107a** respectively, resulting in the deduction of the stereochemistry of the two latter compounds.

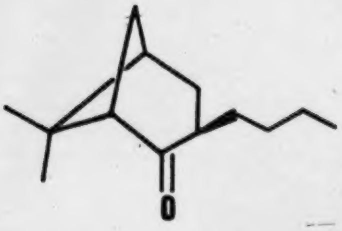
In principle, an allylic pivalate could couple with a diorganocuprate in two different ways involving either the α-carbon bearing the pivaloxy group to give the "S_N2"-type product or the γ-carbon with simultaneous migration of the double bond to give the "S_N2'"-type product. An examination of the experimental results showed that the coupling proceeded with a high degree of regioselectivity with both the lithium and the magnesium-containing reagents. More interestingly, a complementary mode of selectivity was displayed by these two types of reagents. With lithium diorganocuprates, the general mode is the displacement at the α-carbon as indicated by the predominant formation of the "S_N2"-type product in all the reactions studied except one (Entry 9) in which the double bond of the allylic pivalate system is terminal. With the magnesium organocopper reagents, the major product obtained without any exception was found to be that resulting from γ-attack. It is also noteworthy that the double bond geometry remained intact whenever the reaction proceeded _via_ α-substitution (Entries 1, 2, 11 and 12).

The ability of allylic pivalates to undergo efficient coupling with both the lithium and the magnesium organocopper reagents with reversal of regiochemistry promises to have broad synthetic utility. Other allylic esters[55] so far explored often show inconsistent and thus rather unpredictable regioselectivity when subjected to coupling with lithium organocopper reagents and in general do not couple effectively with magnesium organocopper reagents. This is further substantiated by the following experiments. Farnesyl acetate (**110**) was treated with ethylmagnesium bromide-cuprous iodide (2:1) complex under the same conditions used for the corresponding pivalate (Entry 4). Upon completion of the reaction (1 h), trienes **89** and **90** were isolated in 4:3 ratio and in 27% total yield. Similarly, treatment of farnesyl acetate (**110**) with n-BuMgBr-CuI (2:1) complex gave a total of 43% yield of two coupling products **91** and **92** in a ratio of 4:3. These results are considerably inferior to those obtained for farnesyl pivalate (Entries 4 and 6) in terms of yield and regioselectivity.

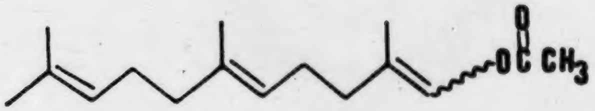
Although the mechanism of the coupling reactions involving organocopper reagents is far from clear, the observed regiochemical reversal might be rationalized by invoking the preferential complexation of the lithium organocopper reagent with the carbonyl oxygen atom and that of the magnesium organocopper reagent with the allylic oxygen atom followed, in each case, by the carbon-



108



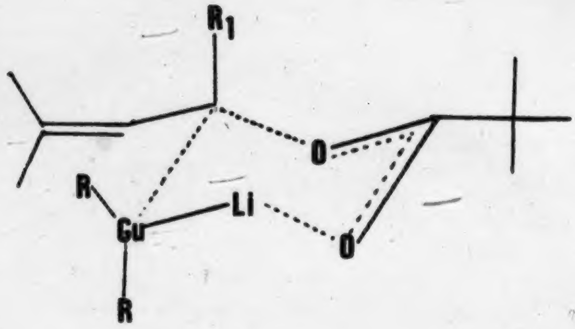
109



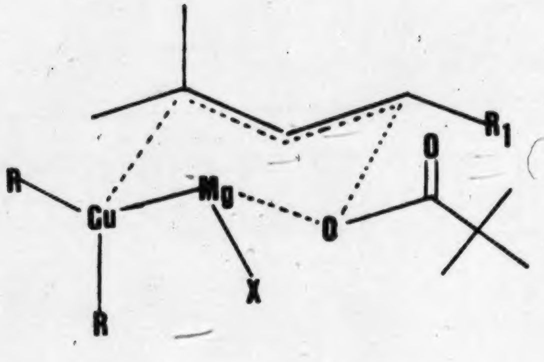
110

carbon bond formation via a six-membered ring transition state as indicated respectively in formulas **111** and **112**.

In conclusion, the annelation of β-keto thiolesters provides a viable alternative to that of the oxygen analogs to facilitate the preparation of fused and bridged polycyclic compounds. Making use of some special properties of the thiolester functionality, several applications of the annelation products in organic synthesis have also been successfully demonstrated. Furthermore, an extension of an interesting finding during the course of these studies resulted in the development of a new coupling process in which the carbon-carbon bond formation is facilitated by the use of an allylic pivalate as the reactant and the regioselectivity (S_N2- or S_N2'-type) can be controlled by merely selecting a suitable organocopper reagent in the form of lithium or magnesium complex.


R1
O
Li
O
R
Cu
R

111


R1
O
R
Cu
Mg
O
X
R

112

EXPERIMENTAL

General

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses were performed by the microanalytical laboratory of this department. Infrared (ir) spectra were recorded on a Perkin-Elmer model 457 or Nicolet 7-199 FT-IR spectrophotometer. Unless otherwise stated, samples were run as a thin film or as a chloroform solution against a blank chloroform cell. Proton nuclear magnetic resonance (^{1}Hmr) spectra were recorded on a Varian HA-100, HA-100/Digilab, Bruker WH-80, Bruker WH-200 and WH-400 spectrometers and, except otherwise stated, were obtained on solutions in deuterochloroform with tetramethylsilane as internal reference. Carbon-13 nuclear magnetic resonance (^{13}Cmr) spectra were recorded on Bruker WH-200 and WH-400 spectrometers and were obtained on solutions in deuterochloroform using tetramethylsilane as internal reference. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br. = broad. Mass spectra (ms) were recorded using A.E.I. model MS 9, MS 12 or MS 50 mass spectrometers. Concentrations of solvent systems used in column chromatography are given by volumes, e.q. 10% ether in hexane means 10 parts of diethyl ether to 90 parts hexane by volume. All the isolated products were found to be homogeneous on thin-layer chromatogram in various solvent systems.

Materials

Ether, benzene and 1,2-dimethoxyethane used for reactions were freshly distilled from lithium aluminum hydride. Pyridine was distilled from potassium hydroxide and stored over barium oxide. Argon and nitrogen were passed through a purification train of Fieser's solution, concentrated sulfuric acid and potassium hydroxide pellets. Silica gel, 0.040-0.063 mm particle size, 230-400 mesh ASTM, was used as adsorbent for flash chromatography and silica gel, 60-120 mesh, was used as adsorbent for column chromatography. Thin-layer chromatography was carried out by using Merck silica gel G (type 60). Unless otherwise stated, anhydrous magnesium sulfate was used for drying organic solutions. Commercially available sodium hydride (50% dispersion in oil) was used without washing. Commercially available methyl vinyl ketone (MVK), ethyl vinyl ketone (EVK), and acrolein were distilled before use. Ethyllithium was made from lithium metal and ethyl bromide according to the described procedure.[56] Methyllithium and _n_-butyllithium were obtained from commercial sources. All the Grignard reagents used were freshly prepared from its corresponding alkyl halide with magnesium turnings according to the standard procedure.[57] Geraniol, farnesol, (±)-periyllyl alcohol, and (-)-Myrtenal were also obtained from commercial sources.

2-Methyl-6-methylthiocarbonylcyclohexanone (**31**)

2-Methylcyclohexanone (3 g, 26.87 mmol) and S,S'-dimethyl dithiocarbonate (6.588 g, 53.74 mmol) were dissolved in 1,2-dimethoxyethane (30 mL). Sodium hydride (50% oil dispersion; 2.58 g, 53.74 mmol) was added to the solution. The mixture was heated to 80°C with stirring for 12 h under an argon atmosphere. After cooling to room temperature, it was poured into ice-cold 1 N aqueous hydrochloric acid (100 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were washed with water, dried ($MgSO_4$), filtered and concentrated. Bulb-to-bulb distillation of the crude material at 70°C (oven temperature)/1.0 torr gave the β-keto thiolester **31** (4.24 g; 85% yield): ir 1710 (ketone C=O) and 1675 cm^{-1} (thiolester C=O); ms M^+ 186.0717 (calcd. for $C_9H_{14}O_2S$:

186.0714); ^{1}Hmr (CCl_4) δ 3.51 (m, 1H, -COCHCO-), 2.32 (s, 3H, $-SCH_3$), and 1.18 (d, 3H, J = 8 Hz, $-CHC\underline{H_3}$).

2-Ethylthiocarbonyl-2-(3-oxobutyl)cyclohexanone (**32**)

DABCO (497 mg, 4.43 mmol) and methyl vinyl ketone (311 mg, 4.43 mmol) were added to a solution of β-keto thiolester **29** (690 mg, 3.7 mmol) in 1,2-dimethoxyethane (15 mL). After stirring at room temperature under a nitrogen atmosphere for 24 h, the reaction mixture was acidified with a solution of 1 N aqueous hydrochloric acid (50 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane gave the Michael adduct **32** (944 mg; 100% yield): ir 1712 (ketone C=O) and 1665 cm^{-1} (thiolester C=O); ms M^+ 256.1132 (calcd. for $C_{13}H_{20}O_3S$: 256.1132); ^{1}Hmr (CCl_4) 2.88 (q, 2H, J = 7 Hz, $-SC\underline{H_2}CH_3$), 2.04 (s, 3H, $-COCH_3$), and 1.26 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H_3}$).

2-Ethylthiocarbonyl-2-(3-oxopentyl)cyclohexanone (**33**)

DABCO (666 mg, 5.9 mmol) was dissolved in 1,2-dimethoxyethane (20 mL) at room temperature under an argon atmosphere. β-Keto thiolester **29** (762 mg, 4.1 mmol) and EVK (499 mg, 5.9 mmol) were added. After stirring for 20 h, the reaction mixture was poured into 1 N aqueous hydrochloric acid (50 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were washed with water, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane afforded the Michael adduct **33** (974 mg; 88% yield): ir 1713 (ketone C=O) and 1665 cm^{-1} (thiolester C=O); ms M^+ 270.1290 (calcd. for $C_{14}H_{22}O_3S$: 270.1289); ^{1}Hmr (CCl_4) δ 2.88 (q, 2H, J = 7 Hz, $-SC\underline{H_2}CH_3$), 1.25 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H_3}$), and 0.96 (t, 3H, J = 8 Hz, $-COCH_2C\underline{H_3}$).

2-Ethylthiocarbonyl-2-(3-oxopropyl)cyclohexanone (**34**)

DABCO (553 mg, 4.9 mmol) and β-keto thiolester **29** (741 mg, 3.98 mmol) were dissolved in 1,2-dimethoxyethane (10 mL) at room temperature under a nitrogen atmosphere. Acrolein (268 mg, 4.8 mmol) was added to this solution and the reaction mixture stirred for 12 h. It was then poured into a solution of 1 N aqueous hydrochloric acid (50 mL). The resulting solution was extracted with dichloromethane (3 x 20 mL). The extracts were washed with water, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane gave thiolester aldehyde **34** (847 mg; 88% yield): ir 2876, 2732 (-CHO), 1720 (ketone and aldehyde C=O), 1680 and 1670 cm^{-1} (thiolester C=O); ms m/e 181.0866 (M$^+$-61, calcd. for $C_{10}H_{13}O_3$: 181.0865), 153.0904 (M$^+$-89, calcd. for $C_9H_{13}O_2$: 153.0916) and 137.0964 (base peak; M$^+$-105, calcd. for $C_9H_{13}O$: 137.0966); ^{1}Hmr (CCl_4) δ 9.71 (t, 1H, J = 1 Hz, -CHO), 2.89 (q, 2H, J = 7 Hz, $-SC\underline{H_2}CH_3$), and 1.27 (t, 3H, J = 7 Hz, $-SCH_2\underline{CH_3}$); *Anal.* Calcd. for $C_{12}H_{18}O_3S$: C 59.48, H 7.59, S 13.23. Found: C 59.65, H 7.58, S 13.29.

2-Ethylthiocarbonyl-2-(3-oxobutyl)cyclopentanone (35)

DABCO (234 mg, 2.08 mmol) and MVK (146 mg, 2.08 mmol) were added to a solution of β-keto thiolester **30** (300 mg, 1.74 mmol) in 1,2-dimethoxyethane (6 mL). The reaction mixture was stirred at 0°C for 3 h under a nitrogen atmosphere and poured into 1 N aqueous hydrochloric acid (30 mL). The resulting solution was extracted with dichloromethane (3 x 20 mL). The extracts were washed with water, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 5% ether in hexane afforded the Michael adduct **35** (421 mg; 100% yield): ir 1744 (five-membered ring ketone C=O), 1716 (ketone C=O), and 1665 cm^{-1} (thiolester C=O); ms M^+ 242.0984 (calcd. for $C_{12}H_{18}O_3S$: 242.0977); ^{1}Hmr (CCl_4) δ 2.84 (q, 2H, J = 7 Hz, $-SC\underline{H_2}CH_3$), 2.04 (s, 3H, $-COCH_3$), and 1.22 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H_3}$).

6-Methyl-2-methylthiocarbonyl-2-(3-oxobutyl)cyclohexanone (36)

DABCO (448 mg, 4 mmol) was dissolved in 1,2-dimethoxyethane (20 mL) at room temperature under an argon atmosphere. β-Keto thiolester **31** (620 mg, 3.3 mmol) and EVK (280 mg, 4 mmol) were added. After stirring for 16 h, the reaction mixture was poured into 1 N aqueous hydrochloric acid (50 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane afforded a diastereomeric mixture of the Michael adducts **36** (819 mg; 97% yield): ir 1718, 1705 (ketone C=O) and 1664 cm^{-1} (thiolester C=O); ms m/e 209.1176 (base peak; M^+-47, calcd. for $C_{12}H_{17}O_3$: 209.1177) and 181.1227 (M^+-75, calcd. for $C_{11}H_{17}O_2$: 181.1228). The ^{1}Hmr (CCl_4) spectrum showed two sets of signals in 10:1 ratio; a major set of signals at δ 2.26 (s, 3H, $-SCH_3$), 2.04 (s, 3H, $-COCH_3$), and 0.96 (d, 3H, J = 7 Hz, $-\overset{|}{C}HC\underline{H}_3$); a minor set of signals at δ 2.29 (s, 3H, $-SCH_3$), 2.09 (s, 3H, $-COCH_3$), and 0.95 (d, 3H, J = 7Hz, $-\overset{|}{C}HC\underline{H}_3$).

6-Methyl-2-methylthiocarbonyl-2-(3-oxopentyl)cyclohexanone (37)

DABCO (291 mg, 2.6 mmol) and EVK (200 mg, 2.4 mmol) were added to a solution of β-keto thiolester **31** (372 mg, 2.0 mmol) in 1,2-dimethoxyethane (10 mL) at room temperature under a nitrogen atmosphere. After stirring for 24 h, the reaction mixture was poured into ice-cold 1 N aqueous hydrochloric acid (50 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane afforded the Michael adducts **37** (540 mg; 100% yield): ir 1714 (ketone C=O) and 1670 cm^{-1} (thiolester C=O); ms m/e 223.1334 (M^+-47, calcd. for $C_{13}H_{19}O_3$: 223.1334) and 195.1386 (M^+-75, calcd. for $C_{12}H_{19}O_2$: 195.1385). ^{1}Hmr (CCl_4) δ 2.28 (s, 3H, $-SCH_3$), 0.98 (t, 3H, J = 8 Hz, $-CH_2C\underline{H}_3$), and 0.97 (d, 3H, J = 6 Hz, $-\overset{|}{C}HC\underline{H}_3$).

6-Methyl-2-methylthiocarbonyl-2-(3-oxopropyl)cyclohexane (**38**)

DABCO (269 mg, 2.4 mmol) was dissolved in 1,2-dimethoxylethane (12 mL) at room temperature under an argon atmosphere. β-Keto thiolester **31** (370 mg, 1.99 mmol) and acrolein (134 mg, 2.4 mmol) were added. After stirring overnight, the reaction mixture was poured into 1 N aqueous hydrochloric acid (50 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were washed with water, dried, filtered and concentrated. Bulb-to-bulb distillation of the crude residue at 90°C (oven temperature)/2 torr gave a diastereomeric mixture of thiolester aldehydes **38** (424 mg; 88% yield): ir 2862, 2720 (-CHO), 1720 (aldehyde C=O), 1708 (ketone C=O) and 1664 cm^{-1} (thiolester C=O); ms M^+ 242.0969 (calcd. for $C_{12}H_{18}O_3S$: 242.0976); ^{1}Hmr (CCl_4) δ 9.71 (t, 1/5H, J = 2 H, -CHO), 9.69 (t, 4/5H, J = 2 H, -CHO), 2.29 (s, 3/5H, $-SCH_3$), 2.27 (s, 2 2/5H, $-SCH_3$), 1.00 (d, 2 2/5H, J = 7 Hz, $-\overset{|}{C}HC\underline{H_3}$), and 0.96 (d, 3/5H, J = 7 Hz, $-\overset{|}{C}HC\underline{H_3}$).

6-Ethylthiocarbonylbicyclo[4.4.0]dec-1-en-3-one (**39**)

A solution of the diketo thiolester **32** (2.04 g, 7.97 mmol) in benzene (2 mL) was added to a solution of p-toluenesulfonic acid dihydrate (208 mg, 1 mmol) in benzene (200 mL). The reaction mixture was heated under reflux with a Dean-Stark water separator for 10 h under an argon atmosphere. After cooling to room temperature, saturated aqueous $NaHCO_3$ solution (20 mL) was added. The organic layer was separated and the aqueous layer was extracted again with dichloromethane (3 x 20 mL). The extracts were washed with water, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 20% ether in hexane gave enone **39** (1.843 g; 98% yield): ir 1687 (ketone C=O), 1670 (thiolester C=O), and 1618 cm^{-1} (C=C); ms M^+ 238.1030 (calcd. for $C_{13}H_{18}O_2S$: 238.1028); ^{1}Hmr (CCl_4) δ 5.92 (s, 1H, =CH-), 2.89 (q, 2H, J = 8 Hz, $-S\underline{CH_2}CH_3$), and 1.26 (t, 3H, J = 8 Hz, $-SCH_2C\underline{H_3}$); Anal. Calcd. for $C_{13}H_{18}O_2S$: C 65.51, H 7.61, S 13.65. Found: C 65.88, H 7.66, S 13.65.

6-Ethylthiocarbonyl-2-methylbicyclo[4.4.0]dec-1-en-3-one (**40**)

A solution of the diketo thiolester **33** (407 mg, 1.51 mmol) in benzene (1 mL) was added to a solution of p-toluenesulfonic acid (88 mg, 0.51 mmol) in benzene (100 mL). The reaction mixture was heated under reflux with a

Dean-Stark water separator for 20 h under an argon atmosphere. It was then cooled to room temperature and a saturated aqueous $NaHCO_3$ solution (20 mL) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 25% ether in hexane gave enone **40** (380 mg; 100% yield): ir 1675, 1667 (ketone and thiolester C=O), and 1612 cm^{-1} (C=C); ms M^+ 252.1184 (calcd. for $C_{14}H_{20}O_2S$: 252.1186); ^{1}Hmr (CCl_4) δ 2.85 (q, 2H, J = 7 Hz, $-SC\underline{H_2}CH_3$), 1.81 (s, 3H, $=\overset{|}{C}CH_3$), and 1.23 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H_3}$).

6-Ethylthiocarbonylbicyclo[4.3.0]non-1-en-3-one (**41**)

A solution of the diketo thiolester **35** (420 mg, 1.74 mmol) in benzene (4 mL) was added to a solution of p-toluenesulfonic acid (82 mg, 0.47 mmol) in benzene (100 mL). The resulting mixture was heated under reflux with a Dean-Stark water separator for 12 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was made basic with saturated $NaHCO_3$ solution (50 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 20% ether in hexane afforded enone **41** (251 mg; 90% yield): ir 1666 (ketone and thiolester C=O) and 1640 cm^{-1} (C=C); ms M^+ 224.0869 (calcd. for $C_{12}H_{16}O_2S$: 224.0871); ^{1}Hmr (CCl_4) δ 5.91 (t, 1H, J = 2 Hz, =CH-), 2.84 (q, 2H, J = 7 Hz, $-SC\underline{H_2}CH_3$), and 1.22 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H_3}$).

5-Ethylthiocarbonyl-2-methylbicyclo[3.3.1]non-2-en-9-one (42)

To a solution of concentrated sulfuric acid (0.2 mL) in benzene (2 mL) at 2-4°C, was added the diketo thiolester **32** (155 mg, 0.6 mmol). The reaction mixture was stirred for 30 min and poured into ice-cold water (20 mL). The resulting solution was extracted with ether (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane gave enone **42** (137 mg; 95% yield): ir 1721 (ketone C=O) and 1669 cm^{-1} (thiolester C=O); ms M^+ 238.1026 (calcd. for $C_{13}H_{18}O_2S$: 238.1028); ^{1}Hmr (CCl_4) δ 5.65 (m, 1H, =CH-), 2.88 (q, 2H, J = 7 Hz, -SC$\underline{H}_2$CH$_3$), 1.70 (dd, 3H, J = 4, J' = 2 Hz, =$\overset{|}{C}$CH$_3$), and 1.25 (t, 3H, J = 7 HZ, -SCH$_2$C$\underline{H}_3$).

2-Ethyl-5-ethylthiocarbonylbicyclo[3.3.1]non-2-en-9-one (**43**)

To a solution of concentrated sulfuric acid (0.6 mL) in benzene (5 mL) at 2-4°C, was added the diketo thiolester **33** (256 mg, 0.95 mmol). The reaction mixture was stirred for 1.5 h under an argon atmosphere, poured into ice-cold water (50 mL) and extracted with dichloromethane (3 x 15 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane gave enone **43** (227 mg; 95% yield): ir 1725 (ketone C=O) and 1672 (thiolester C=O); ms M$^+$ 252.1193 (calcd. for $C_{14}H_{20}O_2S$: 252.1184); ^{1}Hmr (CCl$_4$) δ 5.61 (m, 1H, =CH-), 2.84 (q, 2H, J = 7 Hz, -SC$\underline{H}_2$CH$_3$), 1.23 (t, 3H, J = 7 Hz, -SCH$_2$C$\underline{H}_3$), and 1.01 (t, 3H, J = 8 Hz, -CH$_2$C$\underline{H}_3$).

5-Ethylthiocarbonyl-2-methylbicyclo[3.2.1]oct-2-en-8-one (**44**)

Diketo thiolester **35** (125 mg, 0.52 mmol) was dissolved in anhydrous dichloromethane (2.5 mL) and a small amount of anhydrous magnesium sulfate (50 mg) was added. To this mixture at 0°C, concentrated sulfuric acid (0.23 mL) was added. After stirring for 1 h under a nitrogen atmosphere, the reaction mixture was poured into ice-cold water (30 mL) and extracted with dichloromethane (3 x 10 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 5% ether in hexane afforded starting material **44** (41 mg; 33% recovery). Further elution with 10% ether in hexane gave enone **27** (41 mg; 35% yield): ir 1756 (ketone C=O) and 1669 cm^{-1} (thiolester C=O); ms M^+ 224.0868 (calcd. for $C_{12}H_{16}O_2S$: 224.0871); ^{1}Hmr (CCl_4) δ 5.26 (br.s, 1H, =CH-), 2.88 (q, 2H, J = 2 Hz, $-SC\underline{H_2}CH_3$), 1.77 (dd, 3H, J = 2, J' = 1 Hz, $=\overset{|}{C}CH_3$), and 1.25 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H_3}$).

1,2-Dimethyl-5-methylthiocarbonylbicyclo[3.3.1]non-2-en-9-one (**45**)

To a solution of concentrated sulfuric acid (0.4 mL) in benzene (2 mL) at 2-4°C, was added the diketo thiolester **36** (146 mg, 0.56 mmol). The reaction mixture was stirred for 1 h under an argon atmosphere, poured into ice-cold water (50 mL) and extracted with dichloromethane

(3 x 10 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane gave enone **45** (133 mg; 100% yield): ir 1716 (ketone C=O) and 1672 cm^{-1} (thiolester C=O); ms M$^+$ 238.1024 (calcd. for $C_{13}H_{18}O_2S$: 238.1027); ^{1}Hmr (CCl_4) δ 5.65 (m, 1H, =CH-), 2.28 (s, 3H, -SCH_3), 1.62 (t, 3H, J = 2 Hz, =$\overset{|}{C}CH_3$), and 1.04 (s, 3H, -CH_3).

2-Ethyl-1-methyl-5-methylthiocarbonylbicyclo[3.3.1]non-2-en-9-one (**46**)

To a solution of concentrated sulfuric acid (0.5 mL) in benzene (4 mL) at 4-5°C, was added the diketo thiolester **37** (220 mg, 0.81 mmol). The reaction mixture was stirred for 1 h under an argon atmosphere, poured into ice-cold water (50 mL) and extracted with dichloromethane (3 x 10 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane afforded enone **46** (165 mg; 81% yield): ir 1716 (ketone C=O) and 1672 cm^{-1} (thiolester C=O); ms M$^+$ 252.1186 (calcd. for $C_{14}H_{20}O_2S$: 252.1184); ^{1}Hmr (CCl_4) δ 5.65 (m, 1H, =CH-), 2.28 (s, 3H,

$-SCH_3$), 1.09 (s, 3H, $-CH_3$) and 1.04 (t, 3H, J = 8Hz, $-CH_2C\underline{H}_3$).

5-Hydroxymethyl-2-methylbicyclo[3.3.1]non-2-en-9-one (**52**)

A solution of enone **42** (130 mg, 0.55 mmol) in benzene (1 mL) was added to a suspension of Raney-nickel (1.5 mL, settled volume) in benzene (2 mL). The mixture was stirred for 30 min at room temperature under a nitrogen atmosphere and filtered. The residue was washed thoroughly with 98% ethanol (15 mL). Concentration of the filtrate gave the crude product which was purified by column chromatography on silica gel. Elution with a solution of 40% ether in hexane afforded alcohol **52** (88 mg; 88% yield): ir 3460 (OH), 1711 (C=O), and 1675 cm^{-1} (C=C); ms M^+ 180.1151 (calcd. for $C_{11}H_{16}O_2$: 180.1150); ^{1}Hmr (CCl_4) δ 5.61 (m, 1H, =CH-), 3.32, 3.21 (both d, 1H each, J = 22 Hz each, $-C\underline{H}_2OH$), and 1.67 (br.s, 3H, $=\overset{|}{C}CH_3$).

5-Hydroxymethyl-1,2-dimethylbicyclo[3.3.1]non-2-en-9-one (**53**)

A solution of the enone **45** (133 mg, 0.56 mmol) in benzene (2 mL) was added to a suspension of Raney-nickel (2 mL, settled volume) in benzene (2 mL). The mixture was stirred for 30 min at room temperature under an argon atmosphere and filtered. The residue was washed thoroughly with 98% ethanol (12 mL). Concentration of the filtrate gave the crude material which was purified by column chromatography on silica gel. Elution with a solution of 40% ether in hexane gave alcohol **53** (97 mg; 89% yield): ir 3480 (OH) and 1696 cm^{-1} (C=O); ms M^+ 194.1303 (calcd. for $C_{12}H_{18}O_2$: 194.1306); ^{1}Hmr (CCl_4) δ 5.64 (m, 1H, =CH-), 3.33, 3.22 (both d, 1H each, J = 22 Hz each, -$\underline{CH_2}$OH), and 1.40 (dd, 3H, J = 2, J' = 2 Hz, $=\overset{|}{C}CH_3$), and 1.05 (s, 3H, -CH_3).

2-Ethyl-5-hydroxymethyl-1-methylbicyclo[3.3.1]non-2-en-9-one (**54**)

A solution of the enone **46** (135 mg, 0.54 mmol) in benzene (2 mL) was added to a suspension of Raney-nickel (2 mL, settled volume) in benzene (2 mL). The mixture, after stirring for 30 min at room temperature under an argon atmosphere, was filtered and the residue was washed thoroughly with 98% ethanol (15 mL). Concentration of the filtrate gave the crude product which was purified by column chromatography on silica gel. Elution with a solution of 40% ether in hexane gave alcohol **54** (94 mg; 84% yield): ir 3500 (OH) and 1700 cm^{-1} (C=O); ms M^+ 208.1464 (calcd. for $C_{13}H_{20}O$: 208.1463); ^{1}Hmr (CCl_4)

δ 5.62 (m, 1H, =CH-), 3.34, 3.23 (both br.d, 1H each, J = 22 Hz, $-C\underline{H}_2OH$), 1.05 (s, 3H, $-CH_3$), and 1.04 (t, 3H, J = 8 Hz, $-CH_2C\underline{H}_3$).

4-Hydroxymethyl-2-methylbicyclo[3.2.1]oct-2-en-8-one (**55**)

A solution of the enone **44** (87 mg, 0.38 mmol) in benzene (2 mL) was added to a suspension of Raney-nickel (1.2 mL, settled volume) in benzene (5 mL). The mixture, after stirring for 20 min at room temperature under an argon atmosphere, was filtered and the residue was washed thoroughly with 98% ethanol (10 mL). Concentration of the filtrate gave the crude material which was purified by column chromatography on silica gel. Elution with a solution of 40% ether in hexane afforded alcohol **55** (34 mg; 53% yield): ir 3546 (OH), 1742 (C=O) and 1665 cm^{-1} (C=C); ms M^+ 166.0990 (calcd. for $C_{10}H_{14}O$: 166.0993); ^{1}Hmr (CCl_4) δ 5.19 (m, 1H, =CH-), 3.50 (br.s, 2H, $-C\underline{H}_2OH$), and 1.75 (dd, 3H, J = 2, J' = 2 Hz, $=\overset{|}{C}CH_3$).

2-Ethyl-5-hydroxymethylbicyclo[3.3.1]non-2-en-9-one (**56**)

A solution of the enone **43** (92 mg, 0.37 mmol) in benzene (2 mL) was added to a suspension of Raney-nickel (1 mL, settled volume) in benzene (2 mL). After stirring for 15 min at room temperature under an argon atmosphere, the mixture was filtered. The residue was washed thoroughly with 98% ethanol (15 mL) and the filtrate was concentrated. Column chromatography of the crude product on silica gel, eluting with a solution of 50% ether in hexane, afforded alcohol **56** (47 mg; 66% yield): ir 3480 (OH) and 1705 cm^{-1} (ketone C=O); ms M^+ 194.1310 (calcd. for $C_{12}H_{18}O_2$: 194.1306); ^{1}Hmr (CCl_4) δ 5.62 (m, 1H, =CH-), 3.36, 3.25 (both d, 1H each, J = 22 Hz each, $-C\underline{H_2}OH$), and 1.01 (t, 3H, J = 7 Hz, $-CH_2C\underline{H_3}$). Anal. Calcd. for $C_{12}H_{18}O_2$: C 74.19, H 9.34. Found: C 73.85, H 9.42. Further elution with ether-hexane (4:1) solution gave diol **57** (14 mg, 19% yield): ir 3380 cm^{-1} (OH); ms M^+ 196.1464 (calcd. for $C_{12}H_{20}O_2$: 196.1463); ^{1}Hmr (CCl_4) δ 5.38 (m, 1H, =CH-), 3.85 (d, 1H, J = 4 Hz, $-\overset{|}{C}\underline{H}OH$), 3.43 (d, 2H, J = 3 Hz, $-C\underline{H_2}OH$), and 0.98 (t, 3H, J = 8 Hz, $-CH_2C\underline{H_3}$).

6-Ethylthiocarbonyl-3,3-ethylenedithiobicyclo[4.4.0]dec-1-ene (59)

Enone **39** (300 mg, 1.26 mmol) and 1,2-ethanedithiol (0.3 mL, 3.78 mmol) were dissolved in dichloromethane (4 mL) and boron trifluoride etherate (0.5 mL) was added. The reaction mixture was stirred for 18 h at room temperature under an argon atmosphere, poured into 4 N aqueous potassium hydroxide solution (100 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were washed with water, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a soluiton of 10% ether in hexane gave the thioketal **59** (354 mg; 91% yield): ir 1683 (thiolester C=O) and 1674 cm^{-1} (C=C); ms M^+ 314.0839 (calcd. for $C_{15}H_{22}OS_3$: 314.0833); ^{1}Hmr (CCl_4) δ 5.78 (br.s, 1H, =CH-), 3.24 (complex, 4H, $-SCH_2CH_2S-$), 2.81 (q, 2H, J = 8 Hz, $-SC\underline{H_2}CH_3$), and 1.22 (t, 3H, J = 8 Hz, $-SCH_3C\underline{H_3}$).

6-Hydroxymethylbicyclo[4.4.0]dec-1-ene (**60**)

A solution of the thioketal **59** (321 mg, 1.02 mmol) in benzene (3 mL) was added to a suspension of Raney-nickel (6 mL, settled volume) in benzene (5 mL). The mixture, after stirring for 2 h at room temperature under an argon atmosphere, was filtered and the residue was washed thoroughly with 98% ethanol (15 mL). Concentration of the filtrate gave the crude material which was purified by column chromatography on silca gel. Elution with a solution of 10% ether in hexane afforded starting material **60** (32 mg; 10% yield). Further elution with 40% ether in hexane gave alcohol **36** (127 mg; 74 yield) as colorless crystals: mp 66-67°C (ether-pet. ether); ir 3478 (OH) and

1658 cm^{-1} (C=C); ms M^{+} 166.1360 (calcd. for $C_{11}H_{18}O$: 166.1358); ^{1}Hmr (CCl_4) δ 5.50 (br.t, 1H, J = 4 Hz, =CH-), 3.60 (s, 2H, $-CH_2OH$), and 2.49 (s, 1H, -OH). Anal. Calcd. for $C_{11}H_{18}O$: C 79.47, H 10.9; Found: C 79.23, H 10.9.

6-Ethylthiocarbonyl-3,3-ethylenedithio-2-methylbicyclo-[4.4.0]dec-1-ene (**61**)

Enone **40** (320 mg, 1.27 mmol) and 1,2-ethanedithiol (0.32 mL, 3.81 mmol) were dissolved in dichloromethane (4 mL) and boron trifluoride etherate (0.5 mL) was added. The reaction mixture was stirred for 20 h at room temperature under a nitrogen atmosphere, poured into 4 N aqueous potassium hydroxide solution (100 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane gave the thioketal **61** (368 mg; 88% yield): ir 1682 cm^{-1} (C=O); ms M^{+} 328.0987 (calcd. for $C_{16}H_{24}OS_3$: 328.0989); ^{1}Hmr (CCl_4) δ 3.28 (complex, 4H, $-SCH_2CH_2S-$), 2.79 (q, 2H, J = 8 Hz, $-SC\underline{H_2}CH_3$), 1.96 (s, 3H, $=CCH_3$), and 1.20 (t, 3H, J = 8 Hz, $-SCH_2C\underline{H_3}$).

6-Hydroxymethyl-2-methylbicyclo[4.4.0]dec-1-ene (**62**)

A solution of the thioketal **61** (313 mg, 0.95 mmol) in benzene (2 mL) was added to a suspension of Raney-nickel (5 mL, settled volume) in benzene (5 mL). The mixture was stirred for 2.5 h at room temperature under an argon atmosphere and filtered. The residue was washed thoroughly with 98% ethanol (15 mL) and the filtrate concentrated. The crude product was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane gave starting material **37** (47 mg; 15% recovery). Further elution with 50% ether in hexane afforded alcohol **62** (108 mg; 63% yield) as colorless crystals: mp 69-70°C (ether-pet. ether); ir 3360 cm^{-1} (OH); ms M^+ 180.1516 (calcd. for $C_{12}H_{20}O$: 180.1514); ^{1}Hmr (CCl_4) 3.49 (s, 2H, $-C\underline{H_2}OH$) and 1.59 (s, 3H, $=\overset{|}{C}CH_3$). Anal. Calcd. for $C_{12}H_{20}O$: C 79.94, H 11.18. Found: C 79.78, H 11.02.

6-Ethylthiocarbonyl-3,3-ethylenedithiobicyclo[4.3.0]non-1-ene (**63**)

Enone **41** (104 mg, 0.46 mmol) and 1,2-ethanedithiol (0.18 mL, 2.13 mmol) were dissolved in dichloromethane (3 mL) and boron trifluoride etherate (0.5 mL) was added. After stirring for 20 h at room temperature under a nitrogen atmosphere, the reaction mixture was poured into 4 N aqueous potassium hydroxide solution (100 mL) and extracted with dichloromethane (3 x 20 ML). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane gave the thioketal **63** (138 mg; 100% yield): ir 1678 (thiolester C=O) and 1654 cm^{-1} (C=C); ms M$^+$ 300.0675 (calcd. for $C_{14}H_{20}OS_3$: 300.0676); ^{1}Hmr (CCl_4) 5.70 (s, 1 H, =CH-), 3.21 (complex, 4H, $-SCH_2CH_2S-$), 2.86 (q, 2H, J = 8 H, $-SC\underline{H_2}CH_3$), and 1.20 (t, 3H, J = 8 Hz, $-SCH_2C\underline{H_3}$).

6-Hydroxymethylbicyclo[4.3.0]non-1-ene (**64**)

A solution of the thioketal **63** (140 mg, 0.47 mmol) in benzene (2 mL) was added to a suspension of Raney-nickel (4 mL, settled volume) in benzene (5 mL). The reaction mixture was stirred for 40 min at room temperature under an argon atmosphere and filtered. The residue was washed thoroughly with 98% ethanol (15 mL) and the filtrate concentrated to give the crude product which was subjected to column chromatography on silica gel. Elution with a solution of 20% ether in hexane afforded alcohol **64** (62 mg; 88% yield): ir 3374 (OH) and 1682 cm^{-1} (C=C); ms M$^+$

152.1207 (calcd. for $C_{10}H_{16}O$: 152.1201); ^{1}Hmr (CCl_4) 5.36 (m, 1H, =CH-) and 3.32 (m, 2H, -CH$_2$OH).

6-Carboxy-3,3-dimethylbicyclo[4.4.0]dec-1-ene (**66**)

At 0°C, a solution of methyllithium in ether (1.6 M; 10 mL, 16 mmol) was added to a suspension of cuprous iodide (1.6 g, 8.4 mmol) in ether (30 mL) under an argon atmosphere. After stirring for 5 min, the mixture was cooled to -40°C and a solution of enone **39** (476 mg, 2 mmol) in ether (10 mL) was added dropwise. The reaction mixture was stirred for another 2 h and then poured into ice-cold 1 N aqueous hydrochloric acid (200 mL) with vigorous stirring. The resulting solution was filtered through celite 545 and extracted with ether (2 x 40 mL). The separated aqueous layer was again extracted with dichloromethane (3 x 30 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with a solution of 30% ether in hexane afforded carboxylic acid **66** (325 mg; 78% yield) as white crystals: mp 88-88.5°C (ether-pet. ether); ir 3700-2400 (acid OH) and 1700 cm^{-1} (acid C=O); ms M$^+$ 208.1463 (calcd. for $C_{13}H_{20}O_2$: 208.1463); ^{1}Hmr (CCl_4) δ 12.18 (s, 1H, -COOH), 5.19 (s, 1H, =CH-), 0.97 (s, 3H, -CH_3), and 0.91

(s, 3H, $-CH_3$). Anal. Calcd. for $C_{13}H_{20}O_2$: C 74.96, H 9.68. Found: C 74.98, H 9.52.

6-Carbomethoxy-3,3-dimethylbicyclo[4.4.0]dec-1-ene (67)

A mixture of potassium carbonate (743 mg, 5.38 mmol) and carboxylic acid **66** (297 mg, 1.43 mmol) in acetone (5 mL) was stirred at room temperature for 2 h. Methyl iodide (0.6 mL, 9.6 mmol) was added. The resulting mixture was stirred for another 20 h, poured into ice-cold water and extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. Column chromatography of the residue, eluting with a solution of 15% ether in hexane, gave ester **67** (254 mg; 80% yield): ir 1730 (C=O), 1371, and 1362 cm^{-1} (CH_3); ms M^+ 222.1623 (calcd. for $C_{14}H_{22}O_2$: 222.1620); ^{1}Hmr (CCl_4) δ 5.18 (s, 1H, =CH-), 3.61 (s, 3H, $-OCH_3$), 0.94 (s, 3H, $-CH_3$), and 0.91 (s, 3H, $-CH_3$).

6-Carbomethoxy-9,9-dimethylbicyclo[4.4.0]dec-1-en-3-one (72)

DABCO (433 mg, 3.86 mmol) was dissolved in 1,2-dimethoxyethane (5 mL) at room temperature under an argon atmosphere. β-Keto ester **71** (580 mg, 3.15 mmol) and MVK (262 mg, 3.74 mmol) were added. After stirring for 20 h, the resulting mixture was poured into 1 N aqueous hydrochloric acid (50 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude product was purified by flash column chromatography on silica gel. Elution with a solution of 10% ethyl acetate in hexane gave 2-carbomethoxy-5,5-dimethyl-2-(3-oxobutyl)cyclohexanone (581 mg; 73% yield): ir 1732 (ester C=O) and 1710 cm^{-1} (ketone C=O); ms M^{+} 254.1521 (calcd. for $C_{14}H_{22}O_4$: 254.1518); ^{1}Hmr (CCl_4) δ 3.68 (s, 3H, $-OCH_3$), 2.04 (s, 3H, $-COCH_3$), 1.01 (s, 3H, $-CH_3$), and 0.87 (s, 3H, $-CH_3$).

A solution of the above diketo ester (466 mg, 1.83 mmol) in benzene (2 mL) was added to a solution of p-toluenesulfonic acid (90 mg, 0.52 mmol) in benzene (80 mL). After refluxing with a Dean-Stark water separator for 10 h under a nitrogen atmosphere, the reaction mixture was cooled to room temperature and a saturated solution of aqueous sodium bicarbonate (20 mL) was added. The organic layer was separated and the aqueous layer extracted again with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 30% ether in hexane afforded enone **72** (373 mg; 86% yield): ir 1720 (ester C=O), 1680 (C=O) and 1665 cm^{-1} (C=C); ms M^{+}

236.1410 (calcd. for $C_{14}H_{20}O_3$: 236.1412); ^{1}Hmr (CCl_4) δ 5.91 (br.s, 1H, $=CH-$), 3.73 (s, 3H, $-OCH_3$), 2.12 (s, 2H, $=\overset{|}{C}CH_2-$), 1.02 (s, 3H, $-CH_3$), and 0.91 (s, 3H, $-CH_3$).

6-Carbomethoxy-9,9-dimethylbicyclo[4.4.0]dec-1-ene (**73**)

Enone **72** (897 mg, 3.8 mmol) and 1,2-ethanedithiol (1 mL, 11.9 mmol) were dissolved in dichloromethane (10 mL) and boron trifluoride etherate (1 mL) was added. After stirring for 20 h at room temperature under a nitrogen atmosphere, it was poured into 4 N aqueous potassium hydroxide solution (100 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with a solution of 5% ether in hexane afforded the corresponding thioketal (1.07 g; 98% yield): ir 1732 (ester C=O) and 1668 cm^{-1} (C=C); ms M$^+$ 312.1215 (calcd. for $C_{16}H_{24}O_2S_2$: 312.1218); ^{1}Hmr (CCl_4) δ 5.68 (br.s, 1H, $=CH-$), 3.68 (s, 3H, $-OCH_3$), 3.32 (complex, 4H, $-SCH_2CH_2S-$), 1.31 (s, 2H, $=\overset{|}{C}CH_2-$), 0.91 and 0.81 (both s, 3H each, $-\overset{|}{C}(CH_3)_2$).

A solution of the above thioketal ester (625 mg, 2 mmol) in benzene (3 mL) was added to a suspension of Raney-nickel (6 mL, settled volume) in benzene (5 mL).

After stirring for 40 min at room temperature under a nitrogen atmosphere, the reaction mixture was filtered and the residue washed thoroughly with 98% ethanol (15 mL). The filtrate was concentrated and the crude product purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane gave ester **73** (356 mg; 80% yield): ir 1730 (ester C=O) and 1382 cm^{-1} (CH_3); ms M^+ 222.1621 (calcd. for $C_{14}H_{22}O_2$: 222.1620); ^{1}Hmr (CCl_4) δ 5.53 (br.s, 1H, =CH-), 3.68 (s, 3H, $-OCH_3$), 0.90 and 0.80 (both s, 3H each, $-\overset{|}{C}(CH_3)_2$).

Isomerization of Ester 73

Ester **73** (100 mg, 0.45 mmol) and p-toluenesulfonic acid (100 mg, 0.58 mmol) were dissolved in benzene (10 mL). The mixture was heated under reflux with a Dean-Stark water separator for 12 h. After cooling to room temperature, it was poured into a solution of saturated aqueous sodium bicarbonate (20 mL) and extracted with dichloromethane (3 x 10 mL). The extracts were washed with brine, dried, filtered and concentrated. Purification of the residue by column chromatography on silica gel gave a mixture of esters **73** and **67** (100 mg; 100% yield). The ^{1}Hmr spectrum of the mixture showed two sets of signals in 2:1 ratio. The major set was identical with those of the starting material and the minor set attributed to the isomeric ester **67**.

6-Carboxy-2,3,3-trimethylbicyclo[4.4.0]dec-1-ene (**74**)

At 0°C, a solution of methyllithium in ether (1.6 M; 2.12 mL, 3.39 mmol) was added to a suspension of cuprous iodide (323 mg, 1.66 mmol) in ether (10 mL) under a nitrogen atmosphere. After stirring for 5 min, the mixture was cooled to -25°C and a solution of enone **40** (130 mg, 0.49 mmol) in ether (10 mL) was added. The reaction mixture was stirred for an additional period of 4 h and then poured into ice-cold 1 N aqueous hydrochloric acid (100 mL) with vigorous stirring. The resulting solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with a solution of 30% ether in hexane afforded carboxylic acid **74** (102 mg, 94% yield) as white crystals: mp 105-106°C (n-hexane); ir 3450-2620 (carboxylic OH) and 1702 cm^{-1} (C=O); ms M^+ 222.1622 (calcd. for $C_{14}H_{22}O_2$: 222.1620); ^{1}Hmr δ 1.62 (s, 3H, $=\overset{|}{C}CH_3$) and 0.98 (s, 6H, $-\overset{|}{C}(CH_3)_2$).

6-Carboxy-3,3-dimethylbicyclo[4.3.0]non-1-ene (**75**)

At 0°C, a solution of methyllithium in ether (1.6 M; 2.2 mL, 3.52 mmol) was added to a suspension of cuprous iodide (0.35 g, 1.84 mmol) in ether (10 mL) under a nitrogen atmosphere. After stirring for 5 min, the mixture was cooled to -40°C and a solution of enone **41** (92 mg, 0.41 mmol) in ether (10 mL) was added dropwise. The reaction mixture was stirred for 2 h and poured into ice-cold 1 N aqueous hydrochloric acid (100 mL) with vigorous stirring. The resulting solution was filtered through celite 545 and extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 30% ether in hexane gave carboxylic acid **75** (48.5 mg; 61% yield) as white crystals: mp 92.5-93.5°C (ether-pet. ether); ir 3700-2500 (carboxylic OH) and 1702 cm^{-1} (C=O); ms M^+ 194.1304 (calcd. for $C_{12}H_{18}O_2$: 194.1307); ^{1}Hmr (CCl_4) δ 5.21 (br.s, 1H, =CH-), 1.01 (s, 3H, $-CH_3$), and 0.91 (s, 3H, $-CH_3$).

6-Carbomethoxy-3,3-dimethylbicyclo[4.3.0]non-1-ene (**76**)

Potassium carbonate (156.7 mg, 1.13 mmol) was added to a solution of carboxylic acid **75** (44 mg, 0.23 mmol) in acetone (3 mL). The mixture was stirred at room temperature for 2 h and methyl iodide (0.14 mL, 2.26 mmol) was then introduced. The resulting mixture was stirred for an additional period of 24 h, then poured into ice-cold water (50 mL) and extracted with dichloromethane (3 x 10 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 15% ether in hexane afforded a rather volatile ester **76** (22 mg; 46% yield): ir 1732 (C=O) and 1378 cm^{-1} (CH_3); ms M$^+$ 208.1465 (calcd. for $C_{13}H_{20}O_2$: 208.1463); ^{1}Hmr (CCl_4) δ 5.16 (s, 1H, =CH-), 3.68 (s, 3H, $-OCH_3$), 0.98, and 0.90 (both s, 3H each, $-\overset{|}{C}(CH_3)_2$).

6β-Carboethoxy-3β-hydroxy-3α-methylbicyclo[4.4.0]dec-1-ene (**78**) and 6β-Carboethoxy-3α-hydroxy-3β-methylbicyclo-[4.4.0]dec-1-ene (**79**)

(A) Using Methyllithium

Enone ester **77** (444 mg, 2.0 mmol) was dissolved in ether (10 mL) and a solution of methyllithium in ether (1.6 M; 1.25 mL, 2.0 mmol) was added at -78°C under a nitrogen atmosphere. After stirring for 0.5 h, the reaction mixture was poured into a saturated solution of aqueous ammonium chloride (30 mL) and extracted with ether

(2 x 20 mL). The aqueous layer was separated and extracted again with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with 30% ether in hexane afforded alcohol **78** (357 mg; 75% yield): ir 3450 (OH), 1730 (ester C=O), and 1669 cm^{-1} (C=C); ms M^+ 238.1562 (calcd. for $C_{14}H_{22}O_3$: 238.1568); ^{1}Hmr (CCl_4) δ 5.38 (s, 1H, =CH-), 4.10 (q, 2H, J = 8 Hz, $-OC\underline{H_2}CH_3$), 1.23 (t, 3H, J = 8 Hz, $-OCH_3C\underline{H_3}$), and 1.21 (s, 3H, $-CH_3$). Further elution with the same solvent system gave alcohol **79** (103 mg; 22% yield): ir 3460 (OH), 1732 (ester C=O) and 1680 cm^{-1} (C=C); ms M^+ 238.1566 (calcd. for $C_{14}H_{22}O_3$: 238.1568); ^{1}Hmr δ 5.40 (s, 1H, =CH-), 4.13 (q, 2H, J = 8 Hz, $-OC\underline{H_2}CH_3$), 1.25 (t, 3H, J = 8 Hz, $-OCH_2C\underline{H_3}$), and 1.15 (s, 3H, $-CH_3$).

(B) Using Lithium Dimethylcuprate

Methyllithium (1.6 M in ether; 8.57 mL, 13.7 mmol) was added to a suspension of cuprous iodide (1.37 g, 7.2 mmol) in ether (25 mL) at 0°C under an argon atmosphere. After stirring for 5 min, the reaction mixture was cooled to -40°C and a solution of enone ester **77** (444 mg, 2.0 mmol) in ether (10 mL) was added. After stirring for an additional period of 2 h, the reaction mixture was poured into ice-cold 1 N aqueous hydrochloric acid (100 mL) with vigorous stirring. The resulting solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with 30% ether in hexane afforded alcohols **78** (80 mg; 17% yield) and **79** (242 mg; 51% yield).

2-Methyl-4,4a,5,6,7,8-hexahydronaphthalene (**80**)

Sodium hydride (50% oil dispersion; 93 mg, 1.91 mmol) was added to a solution of ester **78** (460 mg, 1.90 mmol) in 1,2-dimethoxyethane (8 mL). The reaction mixture was heated at reflux for 24 h under a nitrogen atmosphere and poured into water (20 mL). The resulting solution was extracted with dichloromethane (3 x 20 mL). The extracts were washed with water, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with hexane gave cyclic diene **80** (165 mg; 59% yield): ir 1667 cm^{-1} (C=C); ms M^+ 148.1250 (calcd. for $C_{11}H_{16}$: 148.1252); ^{1}Hmr δ 5.45 (br.s, 1H, =CH-) and 1.63 (br.t, 3H, J = 2 Hz, $=\overset{|}{C}CH_3$).

1-Methyl-10-oxatricyclo[6.2.2.0^{3,8}]dodec-2-en-9-one (**81**)

Sodium hydride (50% oil dispersion; 145 mg, 3.0 mmol) was added to a solution of hydroxy thiolester **82** (641 mg, 2.52 mmol) in 1,2-dimethoxyethane (10 mL). The reaction mixture was stirred at room temperature under an argon atmosphere for 24 h. It was then poured into water (20 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was a mixture of lactone **81** and cyclic diene **80** (total 457 mg, ca. 2.8:1 by ^{1}Hmr analysis). Attempted separation of these compounds by column chromatography caused the decomposition of lactone **81** to cyclic diene **80**. The following data were recorded for the mixture of **80** and **81**: ir 1750 (lactone C=O) and 1388 cm^{-1} (CH_3); ms m/e 164.1199 (M$^+$ (**81**)-28, calcd. for $C_{11}H_{16}O$: 164.1201) and 148.1233 (M$^+$(**81**)-44 and/or M$^+$ of **80** calcd. for $C_{11}H_{16}$: 148.1252). The ^{1}Hmr spectrum of the crude product showed two sets of signals in a ratio of 2.8:1 by integration. The minor set of signals were identical with those described for compound **80** and the major set was attributed to compound **81** with signals at δ 5.78 (br.s, 1H, =CH) and 1.74 (s, 3H, $-CH_3$).

6β-Ethylthiocarbonyl-3β-hydroxy-3α-methylbicyclo[4.4.0]dec-1-ene (**82**)

Enone **39** (456, 2 mmol) was dissolved in ether (10 mL) and a solution of methyllithium in ether (1.6 M; 1.25 mL, 2 mmol) was added at -78°C under a nitrogen atmosphere. After stirring for 15 min, the reaction mixture was poured into water (20 mL) and extracted with dichloromethane (3 x 20 mL). The extracts was washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with 30% ether in hexane afforded alcohol **82** (447 mg; 88% yield): ir 3460 (OH), 1680 (thioester C=O) and 1661 cm^{-1} (C=C); ms m/e 239.1069 (M^+-15, calcd. for $C_{13}H_{19}O_2S$: 239.1105) and 149.0965 (base peak; M^+-105, calcd. for $C_{10}H_{13}O$: 149.0966); ^{1}Hmr δ 5.58 (s, 1H, =CH-), 2.81 (q, 2H, J = 8 Hz, $-SC\underline{H_2}CH_3$), 2.02 (s, 1H, -OH), 1.24 (t, 3H, J = 8 Hz, $-SCH_2C\underline{H_3}$), and 1.08 (s, 3H, $-CH_3$). Anal. Calcd. for $C_{14}H_{22}O_2S$: C 66.10, H 8.72, S 12.60. Found: C 66.05, H 8.68, S 12.53.

Carboxylic acid **66** from Lactone **81**

Methyllithium (1.6 M in ether; 5.85 mL, 9.37 mmol) was added to a suspension of cuprous iodide (910 mg, 4.79 mmol) in ether (10 mL) at 0°C under a nitrogen atmosphere.

After stirring for 5 min, the mixture was cooled to -40°C and a solution of lactone **81** and diene **80** (457 mg, ~2.8:1) in ether (5 mL) was added. The resulting mixture was stirred for 2 h and poured into ice-cold 1 N aqueous hydrochloric acid (100 mL). The solution was filtered through celite 545 and extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with hexane gave diene **80** (97 mg). Further elution with 30% ether in hexane afforded a carboxylic acid **66** (355 mg; ~85% yield based on **81**).

(E)-3,7-Dimethyl-2,6-octadien-1-yl pivalate (**85**)

Geraniol (625 mg, 4.05 mmol) and pyridine (0.393 mL, 4.86 mmol) were dissolved in ether (8 mL) at 0°C under a nitrogen atmosphere. A solution of pivaloyl chloride (0.748 mL, 6.08 mmol) in ether (10 mL) was added in a dropwise manner. The reaction mixture was stirred for 2 h at 0°C and 10 h at room temperature. It was then acidified with 1 N aqueous hydrochloric acid (20 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with 10% ether in hexane afforded allylic pivalate **85** (964 mg; 100% yield): ir 1730 (ester C=O) and 1668 cm^{-1} (C=C); ms M^+ 238.1927 (calcd. for $C_{15}H_{26}O_2$: 238.1932); ^{1}Hmr 5.31 (br.td, 1H, J = 7, J' = 2 Hz, =CH-CH_2O-), 5.07 (m, 1H, =CH-CH_2-), 4.55 (d, 2H, J = 7 Hz, -CH_2O-), 1.68 (s, 6H, =$C(CH_3)_2$), 1.60 (s, 3H, =$\overset{|}{C}CH_3$) and 1.19 (s, 9H, -$C(CH_3)_3$).

(E)-2,6-Dimethyl-2,6-dodecadiene (**86**)

At 0°C, n-butyllithium (2.4 M in hexane, 3.7 mL, 8.9 mmol) was added to a suspension of cuprous iodide (1.03 g, 5.45 mmol) in ether (10 mL) under a nitrogen atmosphere. After stirring for 5 min, the mixture was cooled to -40°C and a solution of pivalate **85** (352 mg, 1.48 mmol) in ether (10 mL) was added. The reaction mixture was stirred for 2 h and poured into ice-cold 1 N aqueous hydrochloric acid (100 mL) with vigorous stirring. It was then filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with hexane gave alkene **86** (287 mg; 100% yield): ir 1664 (C=C) and 1385 cm^{-1} (CH_3); ms M^+ 194.2031 (calcd. for $C_{14}H_{26}$: 194.2034); ^{1}Hmr δ 5.12

(m, 2H, both =CH-), 1.70 (s, 3H, $=\overset{|}{\mathrm{C}}\mathrm{CH_3}$), 1.60 (s, 6H, 2 x $=\overset{|}{\mathrm{C}}\mathrm{CH_3}$), and 0.91 (t, 3H, J = 7 Hz, $-\mathrm{CH_2C}\underline{\mathrm{H_3}}$); ^{13}Cmr δ 134.6, 131.0, 124.9, 124.5, 39.8, 31.6, 29.6, 27.9, 26.8, 25.6, 22.6, 17.6, 15.9, and 14.0.

2,6-Dimethyl-6-vinyl-2-decene (**87**)

n-Butylmagnesium bromide (0.4 M in ether; 30 mL, 12 mmol) was added to a suspension of cuprous iodide (1.14 g, 6.0 mmol) in ether (10 mL) at 0°C under a nitrogen atmosphere. After stirring for 5 min, a solution of pivalate **85** (476 mg, 2 mmol) in ether (10 mL) was added. The reaction mixture was stirred for 1 h and poured into ice-cold 1 N aqueous hydrochloric acid (100 mL). The resulting solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (30 mL), brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with hexane gave a mixture of alkenes **86** and **87** (339 mg; 87% yield) in 1:3 ratio by ^{1}Hmr integration. Further elution with 10% ether in hexane afforded starting material **85** (38 mg; 8% recovery). Continuing elution with 50% ether in hexane gave geraniol (14 mg; 5% yield). The following data were recorded for the mixture of **86** and **87**: ir 1637 (C=C) and 1372 cm^{-1} (CH_3); ms M^+ 194.2032 (calcd. for $C_{14}H_{26}$: 194.2034). The ^{1}Hmr spectrum of the mixture showed two sets of signals; the minor set was identical with those described for compound **86** and the major attributed to compound **87**: ^{1}Hmr δ 5.69 (dd, 1H, J = 17, J' = 11 Hz, $-\underline{H}C{=}CH_2$), 5.11 (m, 1H, $=C\underline{H}{-}CH_2{-}$), 4.96 (dd, 1H, J = 11, J' = 2 Hz, $-CH{=}C\underline{H}H$), 4.88 (dd, 1H, J = 17, J' = 2 Hz, $-CH{=}CH\underline{H}$), 1.68 (s, 3H, $=\overset{|}{C}CH_3$), 1.58 (s, 3H, $=\overset{|}{C}CH_3$), 0.94 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), and 0.88 (t, 3H, J = 7 Hz, $-CH_2C\underline{H_3}$); the ^{13}Cmr spectrum of the mixture also showed two sets of signals; a minor set for compound **86** (*vide supra*) and a major set for compound **87** with signals at: δ 149.59, 130.86, 125.32, 111.31, 40.89, 40.67, 39.5, 29.6, 26.4, 25.69, 23.62, 22.95, 22.73, 17.6 and 14.1. *Anal.* Calcd. for $C_{14}H_{26}$: C 86.52, H 13.48. Found: C 86.60, H 13.51.

3,7,11-Trimethyl-2,6,10-dodecatrien-1-yl pivalate (**88**)

Farnesol (3.021 g, 13.59 mmol) and pyridine (1.3 mL, 16.08 mmol) were dissolved in ether (60 mL) at 0°C under a nitrogen atmosphere. A solution of pivaloyl chloride (2.51 mL, 20.39 mmol) in ether (10 mL) was added dropwise and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was then acidified with 1

N aqueous hydrochloric acid (30 mL), separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (20 mL), brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane gave a mixture of cis and trans isomers of pivalate **88** (4.1 g; 99% yield) in a 2.5:1 ratio based on gc analysis and ^{1}Hmr integration: ir 1737 (ester C=O) and 1670 cm^{-1} (C=C); ms M$^+$ 306.2557 (calcd. for $C_{20}H_{34}O_2$: 306.2558); ^{1}Hmr δ 5.34 (br.t, 1H, J = 7 Hz, $=C\underline{H}-CH_2-O-$), 5.11 (m, 2H, 2 x =CH-), 4.55 (d, ~10/7H, J = 7 Hz, $=CH-C\underline{H_2}-O-$), 4.52 (d, ~4/7H, $=CH-C\underline{H_2}-O-$), 1.68 (s, 6H, 2 x $=\overset{|}{C}CH_3$), 1.50 (s, 6H, 2 x $=\overset{|}{C}CH_3$), and 1.19 (s, 9H, 3 x $-CH_3$). Anal. Calcd. for $C_{20}H_{34}O_2$: C 78.38, H 11.18. Found: C 78.31, H 11.17.

2,6,10-Trimethyl-2,6,10-tetradecatriene (**89**)

Ethyllithium (0.33 M in pentane; 11.4 mL, 3.76 mmol) was added to a suspension of cuprous iodide (430 mg, 2.26 mmol) in ether (10 mL) at 0°C under a nitrogen atmosphere. After stirring for 5 min, the mixture was cooled to -40°C and a solution of farnesyl pivalate **88** (192 mg, 0.62 mmol) in ether (3 mL) was added. The reaction mixture was stirred for 2 h and poured into ice-cold 1 N aqueous hydrochloric acid (30 mL). The resulting solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide, brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with hexane afforded a mixture of alkenes **89** (138 mg; 95% yield): ir 1660, 1636 (C=C) and 1378 cm^{-1} (CH_3); ms M^+ 234.2348 (calcd. for $C_{17}H_{30}$: 234.2348); ^{1}Hmr δ 5.13 (m, 3H, 3 x =CH-), 1.70, 1.61 (both s, 6H each, both 2 x $=\overset{|}{C}CH_3$), and 0.88 (t, 3H, J = 7 Hz, $-CH_2C\underline{H}_3$). The ^{13}Cmr spectrum showed two sets of signals in 2.5:1 ratio based on integration; a major set with signals at δ 134.99, 134.90, 131.18, 125.26, 124.72, 124.57, 39.83, 32.10, 32.04, 30.11, 26.89, 26.85, 26.69, 25.66, 17.65, 16.01, and 13.79; a minor set with signals at δ 135.09, 135.04, 131.43, 125.53, 125.50, 124.50, 40.16, 26.75, 23.38, 23.06, 17.65, 16.01, and 133.88. Anal. Calcd. for $C_{17}H_{30}$: C 87.10, H 12.90. Found: C 87.30, H 12.91.

(E)-3-Ethyl-3,7,11-trimethyl-1,6,10-dodecatriene (**90**)

Ethylmagnesium bromide (1 M in ether; 6 mL, 6.0 mmol) was added to a suspension of cuprous iodide (685 mg, 3.6 mmol) in ether (15 mL) at 0°C under a nitrogen atmosphere. The mixture was stirred for 5 min and a solution of farnesyl pivalate **88** (306 mg; 1 mmol) in ether (5 mL) was added. After stirring for 1.5 h, it was poured into ice-cold 1 N aqueous hydrochloric acid (100 mL). The resulting solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (30 mL), brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with hexane afforded a mixture of alkenes **89** and **90** (234 mg; 100% yield). The following data were recorded for the mixture of alkenes **89** and **90**: ir 1674, 1646 (C=C) and 1386 cm^{-1} (CH_3); ms M^+ 234.2347 (calcd. for $C_{17}H_{30}$: 234.2348). The ^{1}Hmr spectrum showed two sets of signals in 4:1 ratio based on integration; the minor signals were the same as those described for the mixture of alkenes **89**; the major set was attributed to compound **90** with signals at δ 5.68 (ddd, 1H, J = 17, J' = 11, J" = 5 Hz, $-C\underline{H}=CH_2$), 5.13 (m, 2H, 2 x =CH-), 5.00 (dt, 1H, J = 11, J' = 1.5 Hz,

$=CH\underline{H}$), 4.90 (dt, 1H, J = 17, J' = 1.5 Hz, $=C\underline{H}H$), 1.70 (s, 6H, 2 x $=\overset{|}{C}CH_3$), 1.60 (s, 3H, $=\overset{|}{C}CH_3$), 0.95 (d, 3H, J = 3 Hz, $-CH_3$) and 0.80 (td, 3H, J = 7.5, J' = 1.5 Hz, $-CH_2C\underline{H_3}$). The ^{13}Cmr spectrum showed three sets of signals; two minor sets of signals were identical with those described for alkenes **89**; the major set was due to compound **90** with signals at δ 147.22, 125.94, 124.51, 111.60, 40.79, 40.49, 33.40, 33.09, 22.81, 22.69, 22.08, 17.69, and 8.39.

2,6,10-Trimethyl-2,6,10-hexadecatriene (**91**)

n-Butyllithium (2 M in hexane; 3 mL, 6 mmol) was added to a suspension of cuprous iodide (658 mg, 7.2 mmol) in ether (10 mL) at 0°C under a nitrogen atmosphere. After stirring for 5 min, the mixture was cooled to -40°C and a solution of farnesyl pivalate **88** (306 mg, 1 mmol) was added. The reaction mixture was stirred for 2 h and poured into ice-cold 1 N aqueous hydrochloric acid (50 mL). The resulting solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide, brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with hexane afforded a mixture of alkenes **91** (262 mg; 100% yield): ir 1672 (C=C) and 1388 cm^{-1} (CH_3); ms M$^+$ 262.2660 (calcd. for $C_{19}H_{34}$: 262.2660); ^{1}Hmr δ 5.13 (m, 3H, 3 x =CH-), 1.70, 1.62 (both s, 6H each, both 2 x $=\overset{|}{C}CH_3$), and 0.88 (t, 3H, J = 7 Hz, $-CH_2C\underline{H_3}$). The ^{13}Cmr spectrum showed two sets of signals in 2.5 to 1 ratio based on integration; a major set with signals at δ 134.76, 134.63, 124.90, 124.49, 124.35, 39.78, 32.04, 31.98, 26.69, 26.61, 25.61, 22.65, 17.58, 15.90 and 14.03; a minor set with signals at δ 134.90, 134.84, 131.03, 125.69, 125.19, 124.90, 40.09, 34.58, 32.30, 31.69, 29.86, 23.33, 17.58 and 14.03. *Anal.* Calcd. for $C_{19}H_{34}$: C 86.94, H 13.06. Found: C 86.89, H 13.09.

(*E*)-2,6,10-Trimethyl-10-vinyl-2,6-tetradecadiene (**92**)

n-Butylmagnesium bromide (0.59 M in ether, 11.6 mL, 6.84 mmol) was added to a suspension of cuprous iodide (653 mg, 3.4 mmol) in ether (15 mL) at 0°C under a nitrogen atmosphere. After the mixture was stirred for 10 min, a solution of farnesyl pivalate **88** (350 mg, 1.14 mmol) in ether (5 mL) was added. Stirring was continued for 1 h. The resulting mixture was poured into ice-cold 1 N aqueous hydrochloric acid (50 mL). The solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (20 mL), brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with hexane afforded a mixture of alkenes **91** and **92** (296 mg; 99% yield). The following data were recorded for the mixture of alkenes **91**, and **92**: ir 1670, 1648 (C=C) and 1387 cm^{-1} (CH_3); ms M^+ 262.2660 (calcd. for $C_{19}H_{34}$: 262.2660). The ^{1}Hmr spectrum showed two sets of signals in 6:1 ratio based on integration; the minor signals were the same as those described for the mixture of alkenes **91**; the major set was attributed to compound **92** with signals at δ 5.69 (ddd, 1H, J = 17, J' = 11, J" = 5Hz, $-C\underline{H}=CH_2$), 5.11 (m, 2H, 2 x =CH-), 4.96 (dt, 1H, J = 11, J' = 1.5 Hz, $=CH\underline{H}$), 4.87 (dt, 1H, J = 17, J' = 1.5 Hz, $=C\underline{H}H$), 1.70 (s, 6H, 2 x $=\overset{|}{C}CH_3$), 1.60 (s, 3H, $=\overset{|}{C}CH_3$), 0.94 (d, 3H, J = 3 Hz, $-CH_3$), and 0.88 (t, 3H, J = 7 Hz, $-CH_2C\underline{H_3}$). The ^{13}Cmr spectrum showed three sets of signals; two minor sets of signals were identical with those described for alkenes **91**; a major set was due to compound **92** with signals at δ 147.54, 134.52, 125.99, 125.17, 124.57, 111.35, 41.20, 40.93, 40.71, 32.05, 26.90, 26.39, 25.72, 23.65, 22.86, 22.74, and 14.16. Anal. Calcd. for $C_{19}H_{34}$: C 86.94, H 13.06. Found: C 86.96, H 12.98.

2,6,10-Trimethyl-2,6,10-tridecatriene (**93**)

Methyllithium (1.6 M in ether, 8.12 mL, 13 mmol) was added to a suspension of cuprous iodide (1.48 g, 7.8 mmol) in ether (20 mL) at 0°C under a nitrogen atmosphere. After stirring for 5 min, the mixture was cooled to -20°C and a solution of pivalate **88** (663 mg, 2.16 mmol) in ether (10 mL) was added. The reaction mixture was stirred for 2 h and poured into ice-cold 1 N aqueous hydrochloric acid (100 mL). The resulting solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (30 mL), brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with hexane gave a mixture of alkenes **93** (381 mg; 81% yield): ir 1670 (C=C) and 1382 cm^{-1} (CH_3); ms M^+ 220.2190 (calcd. for $C_{16}H_{28}$: 220.2191); ^{1}Hmr δ 5.12 (m, 3H, 3 x =CH-), 1.70, 1.61 (both s, ~4 2/7H each, 2 x $=\overset{|}{C}CH_3$), 1.69, 1.62 (both s, ~1 5/7H each), 2 x $=\overset{|}{C}CH_3$), 0.94 (t, ~2 1/7H, J = 7 Hz, $-CH_2\underline{CH_3}$), and 0.93 (t, ~6/7H, J = 7 Hz, $-CH_2\underline{CH_3}$). Anal. for $C_{16}H_{28}$: C 87.20, H 12.81. Found: C 87.33, H 12.67. Further elution with 10% ether in hexane gave the starting material **88** (72 mg; 11% recovery).

(*E*)-3,3,7,11-Tetramethyl-1,6,10-dodecatriene (**94**)

Methylmagnesium bromide (0.44 M in ether, 13.6 mL, 6 mmol) was added to a suspension of cuprous iodide (571 mg, 3 mmol) in ether (20 mL) at 0°C under an argon atmosphere. The mixture was stirred for 10 min and warmed to room temperature before a solution of farnesyl pivalate **88** (306 mg, 1 mmol) in ether (5 mL) was added. The reaction mixture was stirred for 8 h, poured into ice-cold 1 N aqueous hydrochloric acid (50 mL). The resulting solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (20 mL), brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with hexane gave a mixture of alkenes **93** and **94** (77 mg; 65% yield based on consumed starting material) in 6:1 ratio based on ^{1}Hmr and ^{13}Cmr integrations. The following data were recorded for the mixture of alkenes **93** and **94**: ir 1645 (C=C) and 1382 cm^{-1} (CH$_3$); ms M$^+$ 220.2183 (calcd. for $C_{16}H_{28}$: 220.2191). The ^{1}Hmr spectrum showed two sets of signals; a minor set of signals was identical with those described for alkenes **93**; a major set was due to compound **94** with signals at δ 5.78 (ddd, 1H, J = 17, J' = 11, J" = 5 Hz, -C$\underline{H}$=CH$_2$), 5.13 (m, 2H, 2 x =CH-), 4.92 (m, 2H, $=CH_2$), 1.70 (br.s, 6H, 2 x $=\overset{|}{C}CH_3$), 1.60 (s, 3H, $=\overset{|}{C}CH_3$), 0.98 and 0.97 (both s, 3H each, both $-\overset{|}{\underset{|}{C}}CH_3$). The ^{13}Cmr spectrum showed three sets of signals; a major set was attributed to compound **94** with signals at δ 148.49, 125.05, 124.51, 110.29, 42.81, 39.79, 26.74, 25.65, 23.31, 21.13, 13.43 and 12.99; two minor sets were due to the mixture of alkenes **93** with signals at δ 128.52, 126.52, 125.85, 43.12, 42.65, 37.68, 36.63, 31.99, 25.90, 23.99, 23.39, 23.19, 22.35, 21.38, 21.21, 17.65, 11.09.

1-Nonen-3-yl pivalate (**95**)

Heptanal (3.4 g, 29.8 mmol) was dissolved in ether (40 mL) under an argon atmosphere. At -78°C, vinyllithium (2.9 M in THF; 10.3 mL, 29.9 mmol) was added to the reaction mixture. The resulting mixture was stirred for 1 h. A solution of pivaloyl chloride (5.5 mL, 44.8 mmol) in ether (10 mL) was added dropwise. The mixture was allowed to warm up slowly to room temperature. After stirring for 20 h, it was poured into a solution of ice-cold 1 N aqueous hydrochloric acid (20 mL), separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (30 mL), brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane gave pivalate **95** (5.517 g; 82% yield): ir 1735 (C=O) and 1648 cm^{-1} (C=C); ms m/e 141.0908 (M^+-85, calcd. for $C_8H_{13}O_2$: 141.0915), 125.1325 (M^+-101, calcd. for C_9H_{17}: 125.1330) and 85.0657 (base peak; M^+-141, calcd. C_5H_9O: 85.0653). ^{1}Hmr δ 5.82 (ddd, 1H, J = 18, J' = 10, J" = 6 Hz, -CH=CH_2), 5.24 (d, 1H, J = 10 Hz, =CHH), 5.18 (dd, 1H, J = 18, J' = 4 Hz, =CHH), 1.19 (s, 9H, $-C(CH_3)_3$), and 0.88 (t, 3H, J = 6 Hz, $-CH_2C\underline{H}_3$). Anal. Calcd. for $C_{14}H_{26}O_2$: C 74.29, H 11.58. Found: C 74.36, H 11.60.

(E)-7-Tridecene (**96**) and (Z)-7-Tridecene (**97**)

(A) Using Lithium Di-n-butylcuprate

n-Butyllithium (2 M in hexane, 6 mL, 12 mmol) was added to a suspension of cuprous iodide (1.37 g, 7.2 mmol) in ether (20 mL) at 0°C under a nitrogen atmosphere. After stirring for 5 min, the mixture was cooled to -40°C and a solution of pivalate **95** (452 mg, 2 mmol) in ether (5 mL) was added. The reaction mixture was stirred for 2 h and poured into ice-cold 1 N aqueous hydrochloric acid (50 mL). The resulting solution was filtered through celite

545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (20 mL), brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with hexane gave a mixture of alkenes **96** and **97** (335 mg; 92% yield). The following data were recorded for the mixture of alkenes **96** and **97**: ir 2928 (C-H) and 1456 (CH_2); ms M^+ 182.2030 (calcd. for $C_{13}H_{26}$: 182.2034); ^{1}Hmr 5.38 (m, 2H, -HC=CH-), 0.90 and 0.89 (both t, 3H each, J = 6 Hz, both $-CH_2C\underline{H_3}$). The ^{13}Cmr spectrum showed two sets of signals in 6:1 ratio based on integration; a major set of signals at δ 130.46, 32.68, 32.66, 31.87, 31.50, 29.73, 29.44, 28.92, 22.72, 22.63 and 14.08; a minor set of signals at δ 129.98, 32.68, 31.64, 29.85, 29.55, 29.08, 27.31, 27.29, 22.72, 22.63 and 14.08.

(B) Using n-Butylmagnesium Bromide and Cuprous Iodide

n-Butylmagnesium bromide (0.4 M in ether, 35.7 mL, 14.3 mmol) was added to a suspension of cuprous iodide (1.63 g, 8.6 mmol) in ether (10 mL) at 0°C under an argon atmosphere. The mixture was stirred for 5 min and a solution of pivalate **95** (538 mg, 2.38 mmol) in ether (3 mL) was added. After stirring for 1 h, the mixture was poured into ice-cold 1 N aqueous hydrochloric acid (50 mL). The resulting solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (20 mL), brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with hexane afforded a mixture of alkenes **96** and **97** (421 mg, 92% yield) in a 2:1 ratio based on integration of the ^{13}Cmr spectrum. Except for the ratio, all the spectral data were identical with those previous described for compounds **96** and **97**.

(_E_)-2,6-Dimethyl-2,6-dodecadien-8-yl Pivalate (**98**)

Citral (794 mg, 5.21 mmol) was dissolved in ether (8 mL) at -78°C under a nitrogen atmosphere. A 2.4 M solution of n-butyllithium in hexane (2.17 mL, 5.21 mmol) was added. The mixture was stirred for 1 h, followed by addition of pivaloyl chloride (0.97 mL, 7.88 mmol) in ether (5 mL). The reaction mixture was stirred at room temperature for 20 h, poured into ice-cold 1 N aqueous hydrochloric acid (30 mL). The resulting solution was extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated.

The crude product was purified by column chromatography on silica gel. Elution with 15% ether in hexane afforded pivalate **98** (1.308 g; 85% yield): ir 1728 (ester C=O) and 1670 cm^{-1} (C=C); ms M^+ 294.2554 (calcd. for $C_{19}H_{34}O_2$: 294.2559); ^{1}Hmr 5.41 (m, 1H, =CH-CH-), 5.13 (m, 1H, -CH-O), 5.04 (m, =CH-CH_2-), 1.20 (s, 9H, -$C(CH_3)_3$), and 0.91 (t, 3H, J = 6 Hz, -$CH_2$$CH_3$).

(*E*)-2,6,8-Trimethyl-2,6-dodecadiene (**99**), (*E*)- and (*Z*)-2,6,6-Trimethyl-2,7-dodecadiene (**100**)

(A) Using Lithium Dimethylcuprate

Methyllithium (1.6 M in ether, 6.43 mL, 10.3 mmol) was added to a suspension of cuprous iodide (1.20 g, 6.3 mmol) in ether (20 mL) at 0°C under a nitrogen atmosphere. After stirring for 5 min, the mixture was cooled to -40°C and a solution of pivalate **98** (505 mg, 1.72 mmol) in ether (5 mL) was added. The reaction mixture was stirred for 2 h and poured into ice-cold 1 N aqueous hydrochloric acid (100 mL). The resulting solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (20 mL), brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with hexane gave a mixture of alkenes **99** and **100** (222 mg; 62% yield). The following data were recorded for the mixture of alkenes **99** and **100**: ir 1662 (C=C) and 1386 cm^{-1} (CH_3); ms m/e 193.1944 (M^+-15, calcd. for $C_{14}H_{25}$: 193.1956) and 151.1486 (M^+-57, calcd. for $C_{11}H_{19}$: 151.1486). There are two sets of signals in the ^{1}Hmr spectrum in 7:1 ratio based on integration; a major set of signals at δ 5.10 (m, 1H, $=C\underline{H}-CH_2-$), 4.88 (d, 1H, $=C\underline{H}-\overset{|}{C}H-$), 1.70 (d, 3H, J = 1.5 Hz, $=\overset{|}{C}CH_3$), 1.59 (d, 6H, J = 1.5 Hz, 2 x $=\overset{|}{C}CH_3$), 0.9 (d, 3H, J = 6 Hz, $-\overset{|}{C}HC\underline{H_3}$), and 0.87 (t, 3H, J = 6 Hz, $-CH_2C\underline{H_3}$); a minor set with signals at δ 5.33 (d, 1H, J = 18 Hz, $-C\underline{H}=CH-$), 5.27 (dt, 1H, J = 18, J' = 6 Hz, $-CH=C\underline{H}-CH_2-$), 1.69 (s, 3H, $=\overset{|}{C}CH_3$), 1.60 (s, 3H, $=\overset{|}{C}CH_3$), 0.98, 0.89 (both s, 3H each, both $-\underset{|}{\overset{|}{C}}CH_3$), and 0.88 (t, 3H, J = 7 Hz, $-CH_2C\underline{H_3}$). _Anal_. Calcd. for $C_{15}H_{28}$: C 86.46, H 13.54. Found: C 86.28, H 13.26.

(B) Using Methylmagnesium Iodide and Cuprous Iodide

Methylmagnesium iodide (0.87 M in ether, 13.8 mL, 12 mmol) was added to a suspension of cuprous iodide (1.37 g, 7.2 mmol) in ether (20 mL) at 0°C under an argon atmosphere. After stirring for 10 min, a solution of pivalate **98** (588 mg, 2 mmol) in ether (5 mL) was added. The reaction mixture was stirred for 5 h and poured into ice-cold 1 N aqueous hydrochloric acid (100 mL). The resulting solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (20 mL), brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with hexane gave a mixture of **99** and **100** (403 mg; 97% yield). The following data were recorded for the mixture of alkenes **99** and **100**: ir 1662, 1645 (C=C), 1381 and 1376 cm^{-1} (CH_3); ms M^+ 208.2185 (calcd. for $C_{15}H_{28}$: 208.2191). The ^{1}Hmr spectrum was the same as that described previously except that the ratio of signals was changed to 1:6. The ^{13}Cmr spectrum showed a major set of signals at δ 131.91, 130.63, 126.25, 125.47, 43.41, 35.66, 32.55, 32.14, 29.85, 27.47, 25.66, 23.56, 22.41, 13.95 and a minor set of signals at δ 133.18, 131.01, 126.81, 124.66, 39.89, 39.57, 30.96, 28.37, 27.12, 26.95, 23.79, 22.99, 22.77, 22.05, and 14.14. Anal. Calcd. for $C_{15}H_{28}$: C 86.46, H 13.54. Found: C 86.45, H 13.54.

Perillyl Pivalate (**101**)

(±)-Perillyl alcohol (1.915 g, 12.6 mmol) and pyridine (1.5 mL, 18.65 mmol) were dissolved in ether (30 mL) at 0°C under an argon atmosphere. A solution of pivaloyl chloride (1.57 mL, 12.8 mmol) in ether (5 mL) was added dropwise. After stirring for 20 h, the reaction mixture was poured into ice-cold 1 N aqueous hydrochloric acid (20 mL). The resulting solution was separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (20 mL), brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with 10% ether in hexane afforded ester **101** (2.98 g, 100% yield): ir 1732 (ester C=O) and 1646 cm^{-1} (C=C); ms M^{+} 236.1777 (calcd. for $C_{15}H_{24}O_2$: 236.1776); ^{1}Hmr δ 5.76 (m, 1H, =CH-), 4.67 (s, 2H, $=CH_2$), 4.46 (s, 2H, $-CH_2-O-$), 1.76 (s, 3H, $=\overset{|}{C}CH_3$), and 1.22 (s, 9H, $-C(CH_3)_3$). Anal. Calcd. for $C_{15}H_{24}O_2$: C 76.23, H 10.23. Found: C 76.34, H 10.22.

4-Isopropenyl-1-pentyl-1-cyclohexene (**102**) and 2-Butyl-4-isopropenyl-1-methylenecyclohexane (**103**)

(A) Using Lithium Di-n-butylcuprate

n-Butyllithium (2 M in hexane, 6 mL, 12 mmol) was added to a suspension of cuprous iodide (1.37 g, 7.2 mmol) in ether (20 mL) at 0°C under an atmosphere of argon. After stirring for 5 min, the mixture was cooled to -40°C and a solution of perillyl pivalate **101** (472 mg, 2 mmol) in ether (2 mL) was added. The reaction mixture was stirred for 2 h and poured into ice-cold 1 N aqueous hydrochloric acid (100 mL). The resulting solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (20 mL), brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with hexane afforded alkene **102** (322 mg; 84% yield): ir 1650 (C=C) and 1381 cm^{-1} (CH_3); ms M^+ 192.1855 (calcd. for $C_{14}H_{24}$: 192.1878); ^{1}Hmr δ 5.41 (m, 1H, =CH-), 4.73 (s, 2H, $=CH_2$), 1.73 (t, 3H, J = 1.5 Hz, $=\overset{|}{C}CH_3$), and 0.89 (t, 3H, J = 6 Hz, $-CH_2\underline{CH_3}$); ^{13}Cmr δ 150.26, 137.78, 120.07, 108.37, 41.39, 37.62, 31.68, 30.87, 28.88, 28.05, 27.50, 22.62, 20.79, and 14.06. Anal. Calcd. for $C_{14}H_{24}$: C 87.42, H 12.58. Found: C 87.45, H 12.58. Further elution with 10% ether in hexane gave the starting material **101** (42.5 mg; 9% recovery).

(B) Using n-Butylmagnesium Bromide and Cuprous Iodide

n-Butylmagnesium bromide (0.635 M in ether, 19 mL, 12 mmol) was added to a suspension of cuprous iodide (1.37 g, 7.2 mmol) in ether (10 mL) at 0°C under an argon atmosphere. The mixture was stirred for 5 min and a solution of pivalate **101** (472 mg, 2 mmol) in ether (10 mL) was added. After stirring for 6 h, the reaction mixture was poured into ice-cold 1 N aqueous hydrochloric acid (100 mL). The resulting solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous hydrochloric acid (20 mL), brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with hexane afforded a mixture of alkenes **102** and **103** (280 mg; 73% yield) in a ratio of 1:11 based on ^{1}Hmr and ^{13}Cmr integrations. The following data were recorded for the mixture of alkenes **102** and **103**: ir 1665, 1645 (C=C) and 1385 cm^{-1} (CH_3); ms m/e 191.1793 (M^+-1, calcd. for $C_{14}H_{23}$: 191.1800) and 135.1178 (M^+-57, calcd. for $C_{10}H_{15}$: 135.1174). The ^{1}Hmr and ^{13}Cmr spectra each showed two sets of signals. The minor sets were identical with those described for **102** (vide supra) and the major sets were attributed to compound **103**: ^{1}Hmr δ 5.68 (t, 2H, J = 1.2 Hz, $=CH_2$), 5.64, 5.60 (both t, 1H each, J = 1.6 Hz, both $=\overset{|}{\mathrm{C}}\mathrm{H}$), 1.70 (s, 3H, $=\overset{|}{\mathrm{C}}\mathrm{CH_3}$), and 0.88 (t, 3H, J = 7.5 Hz, $-\mathrm{CH_2}\underline{\mathrm{CH_3}}$); ^{13}Cmr δ 151.69, 150.19, 108.57, 107.66, 43.40, 39.37, 33.44, 32.09, 31.14, 30.16, 22.77, 20.91, and 14.11.

(1R,5R)-6,6-Dimethyl-2-(1-pivaloyloxylethyl)bicyclo-[3.1.1]hept-2-ene (**104**)

(-)-Myrtenal (2.96 g, 19.7 mmol) was dissolved in ether (30 mL) and methyllithium (1.6 M in ether; 14.8 mL, 23.68 mmol) was added at -78°C under a nitrogen atmosphere. The mixture was stirred for 1 h, followed by addition of a solution of pivaloyl chloride (3.65 mL, 29.64 mmol) in ether (10 mL). The reaction mixture was allowed to warm to room temperature, stirred for 20 h and poured into ice-cold 1 N aqueous hydrochloric acid (20 mL). The resulting solution was separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (20 mL), brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with a solution of 10% ether in hexane gave pivalate **104** (4.704 g; 96% yield): ir 1734 (ester C=O) and 1376 cm^{-1} (CH_3); ms M^+ 250.1928 (calcd. for $C_{16}H_{26}O_2$: 250.1932); ^{1}Hmr δ 5.47 (br.s, 1H, =CH-), 5.21 (q, 1H, J = 8 Hz, $-\overset{|}{C}H-O$), 1.20 (d, 3H, J = 8 Hz, $-\overset{|}{C}HC\underline{H_3}$), 1.18 (s, 9H, $-C(CH_3)_3$), 1.14 and 0.78 (both s, 3H each, $-\overset{|}{C}(CH_3)_2$).

(1R,5R)-6,6-Dimethyl-2-(1-methylpentyl)bicyclo[3.1.1]hept-2-ene (**105**), (*E*)- (**106**), and (*Z*)-(1R,3R,5R)-3-Butyl-2-ethylidene-6,6-dimethylbicyclo[3.1.1]heptane (**107**)

(A) Using Lithium Dibutylcuprate

n-Butyllithium (2 M in hexane; 6.0 mL, 12 mmol) was added to a suspension of cuprous iodide (1.37 g, 7.2 mmol) in ether (20 mL) at 0°C under an argon atmosphere. After stirring for 10 min, the mixture was cooled to -20°C and a solution of pivalate **104** (500 mg, 2 mmol) in ether (5 mL) was added. The reaction mixture was stirred for 2 h and poured into ice-cold 1 N aqueous hydrochloric acid (100 mL). The resulting solution was filtered through celite 545, separated and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (20 mL), brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with hexane gave a mixture of alkenes **105** and **106** (333 mg, 81% yield) in 2.2:1 ratio based on ^{1}Hmr and ^{13}Cmr integrations. The following spectral data were recorded for the mixture of **105** and **106**: ir 2920 (C-H) and 1380 cm^{-1} (CH_3); ms M^+ 206.2025 (calcd. for $C_{15}H_{26}$: 206.2034). The ^{1}Hmr spectrum showed two sets of signals. The major set was due to compound **105**: δ 5.15 (m, 1H, $=\mathrm{C\underline{H}}-$), 1.28, 0.84 (both s, 3H each, $-\overset{|}{\mathrm{C}}(\mathrm{CH_3})_2$), 0.89 (d, 3H, J = 8 Hz, $-\overset{|}{\mathrm{C}}\mathrm{HC\underline{H}_3}$), and 0.88 (t, 3H, J = 8 Hz, $-\mathrm{CH_2C\underline{H}_3}$). The minor set was attributed to compound **106**: δ 5.22 (q, 1H, J = 7 Hz, $=\mathrm{C\underline{H}CH_3}$), 2.81 (t, 1H, J = 6 Hz, $-\overset{|}{\mathrm{C}}\mathrm{\underline{H}}-\overset{|}{\mathrm{C}}=$), 1.58 (dd, 3H, J = 7, J' = 2 Hz, $=\overset{|}{\mathrm{C}}\mathrm{CH_3}$), 1.23 and 0.70 (both s, 3H each, $-\overset{|}{\mathrm{C}}(\mathrm{CH_3})_2$). The ^{13}Cmr spectrum also showed two sets of signals; a major set for compound **105** with signals at δ 146.79, 115.19, 43.51, 42.88, 41.64, 41.29, 31.95, 31.38, 26.45, 21.48, 18.68, 14.14 and 12.48; a minor set for compound **106** with signals at δ 147.99, 116.61, 44.58, 43.57, 40.89, 40.87, 27.81, 26.23, 22.84, 21.59, 14.21 and 12.50.

(B) Using n-Butylmagnesium Bromide and Cuprous Iodide

n-Butylmagnesium bromide (0.635 M in ether; 18.9 mL, 12.0 mmol) was added to a suspension of cuprous iodide (1.37 g, 7.2 mmol) in ether (10 mL) at 0°C under an argon atmosphere. After stirring for 5 min, a solution of pivalate **104** (500 mg, 2 mmol) in ether (5 mL) was added. The reaction mixture was stirred for 1.5 h and poured into ice-cold 1 N aqueous hydrochloric acid (100 mL). The resulting solution was filtered through celite 545, separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The extracts were washed with 1 N aqueous potassium hydroxide (20 mL), brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with hexane gave a mixture of alkenes **105, 106** and **107** (354 mg, 86% yield) in 1:7.5:5 ratio based on ^{1}Hmr and ^{13}Cmr integrations. The following spectral data were recorded for the mixture of alkenes **105, 106** and **107:** ir 2922 (C-H) and 1380 cm^{-1} (CH_3); ms M^+ 206.2031 (calcd. for $C_{15}H_{26}$: 206.2034). The ^{1}Hmr and ^{13}Cmr spectra each showed three sets of signals. The minor and the major signals in each spectrum were identical with those described for **105** and **106** (vide supra). The remaining signals were attributed to compound **107:** ^{1}Hmr δ 4.99 (qd, 1H, J = 7, J' = 2 Hz, $=CHCH_3$), 2.42 (br.t, 1H, J = 6 Hz, $-\overset{|}{C}H-\overset{|}{C}=$), 1.50 (d, 3H, J = 7 Hz, $=\overset{|}{C}CH_3$), 1.20 and 0.62 (both s, 3H each, $-\overset{|}{C}(CH_3)_2$); ^{13}Cmr δ 146.75, 116.36, 52.96, 41.62, 40.59, 27.65, 25.95, 22.86, 21.53, 14.21 and 12.50.

(1R,3S,5R)-3-Butyl-6,6-dimethylbicyclo[3.1.1]heptan-2-one (108)

A mixture of alkenes **105, 106** and **107** (80 mg, 0.39 mmol) was dissolved in dichloromethane (2 mL) and methanol

(2 mL). At -78°C, ozone was bubbled through the mixture until a light blue color was retained. Dimethyl sulfide (0.6 mL, 8.1 mmol) was added. After stirring overnight, the resulting mixture was poured into water and extracted with dichloromethane (3 x 10 mL). The extracts were washed with brine, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 10% ether in hexane, afforded ketone **108** (62 mg, 88% yield): ir 1703 (C=O), 1385 and 1370 cm^{-1} (CH_3); ms M$^+$ 194.1662 (calcd. for $C_{13}H_{22}O$: 194.1670); ^{1}Hmr δ 2.59 (d, 1H, J = 6 Hz, $-\overset{|}{\underset{|}{C}}-\overset{|}{C}HCO-$), 2.52 (m, 1H, $-CH_2-\overset{|}{C}\underline{H}CO-$), 1.33, 0.88 (both s, 3H each, $-\overset{|}{C}(CH_3)_2$), and 0.92 (t, 3H, J = 7.5 Hz, $-CH_2C\underline{H_3}$). Anal. Calcd. for $C_{13}H_{22}O$: C 80.36, H 11.41. Found: C 80.24, H 11.37.

(1R,3R,5R)-3-Butyl-6,6-dimethylbicyclo[3.1.1]heptan-2-one (109)

Ketone **108** (20 mg, 0.1 mmol) was dissolved in methanol (1 mL) and a solution of 1 N aqueous sodium hydroxide (0.5 mL) was added. The reaction mixture was heated at reflux for 16 h. After cooling to room temperature, the resulting mixture was diluted with water (10 mL) and extracted with dichloromethane (3 x 50 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with 10% ether in hexane afforded a mixture of ketones **93** and **94** (20 mg; 100% yield) in a 4:1 ratio based on ^{1}Hmr integration. The following data were recorded for the mixture of ketones **108** and **109**: ir 1701 (C=O), 1385 and 1370 cm^{-1} (CH_3); ms M^+ 194.1668 (calcd. for $C_{13}H_{22}O$: 194.1670). The ^{1}Hmr showed two sets of signals; the major set of signals was the same as that described for ketone **108** and the minor signals for ketone **109** appeared at δ 2.46 (m, 1H, $-CH_2-\overset{|}{C}\underline{H}CO-$), 1.30, 0.73 (both s, 3H each, $-\overset{|}{C}(CH_3)_2$), and 0.93 (t, 3H, J = 7.5 Hz, $-CH_2C\underline{H_3}$).

STUDY II

Studies on the Total Synthesis of α-Patchoulene

INTRODUCTION

α-Patchoulene (**1**) is a tricyclic sesquiterpene which has been isolated from Naraostadys jatamansi[58] and patchouli oil.[59,60] The commercially available patchouli oil is mainly extracts of the leaves of Pogostemon cablin Benth. (syn. P. patchouli Pallet var. suavies Hook), a member of the Labiatae family, and is an important material in the perfume industry.

The structure of α-patchoulene (**1**) was identified by Büchi and co-workers[59] in the early 1960's in connection with their studies on the structure of patchouli alcohol (**2**). Dehydration of patchouli alcohol (**2**) with phosphorus oxychloride in pyridine[61] or via pyrolysis of the corresponding acetate **3**[59] gave a mixture of α- (**1**), β- (**4**) and γ-patchoulene (**5**). It was later found that the dehydration of patchouli alcohol (**2**)[62,63] proceeded with a concomitant Wagner-Meerwein rearrangement reaction. Thus, α-patchoulene (**1**) possesses a tricyclo[5,3,1,$0^{1,5}$]undecane ring system which also forms the parent skeleton of several closely related sesquiterpenes such as α-patcholenone (**6**),[64,65] sugeonol (**7**),[66] cyperene (**8**),[65] and cyperotundone (**9**)[67] isolated from Cyperus rotundus L. tuber oil.

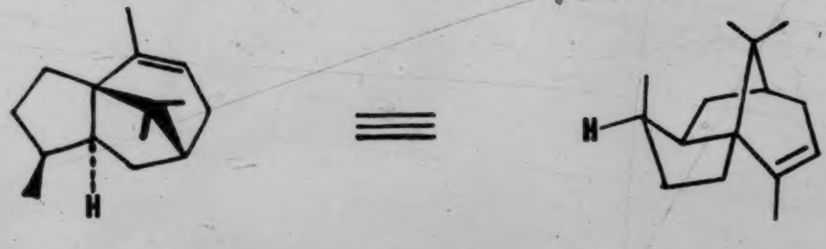
In spite of their unique structural features and commercial importance, α-patchoulene (**1**) and the structurally related sesquiterpenes have drawn little attention to their synthesis. The only total synthesis of α-patchoulene (**1**) known (Scheme 1) was reported more than twenty years ago by Büchi and co-workers[63] who made use of (-)-homocamphor **10** as a starting material. By a short synthetic sequence, this compound was transformed to the tricyclic enone **11** which was then converted to the key intermediate, β-patchoulene oxide (**12**). Treatment of **12** with boron trifluoride etherate followed by deoxygenation and dehydration gave α-patchoulene (**1**).

Recently, an interesting synthetic approach (Scheme 2) to α-patchoulene (**1**) was devised by Deslongchamps and co-workers.[68] They recognized that the carbon frameworks of α-patchoulene (**1**) and α-cedrene (**13**) are very similar. These compounds differ from each other only at the point where ring C of each compound is attached to the fused AB ring system and the locations of the methyl groups on the C rings. It was further recognized that a tetracyclic compound such as **14** could serve as a common intermediate for the synthesis of both α-patchoulene (**1**) and α-cedrene (**13**) by selective cleavage of the cyclopropane ring. Selective cleavage of bond **a** (Path A) is expected to lead eventually to the formation of α-cedrene whereas cleavage of bond **b** (Path B) should give a synthetic intermediate which could be further elaborated to form α-patchoulene. The selective cleavage of bonds **a** and **b** was experimentally carried out under kinetically and thermodynamically controlled conditions respectively. The further conversion of compound **15a** to α-cedrene and **15b** to α-patchoulene, however, remains to be accomplished.

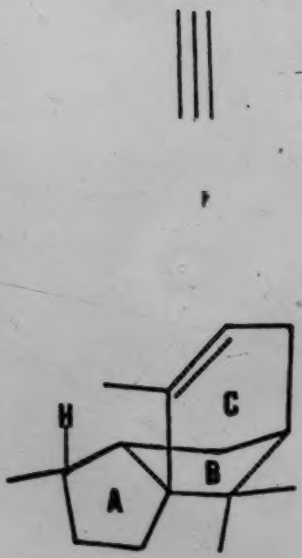
A partial synthesis of cyperene (**8**), cyperotundone (**9**) and α-patchoulenone (**6**) has been achieved by Hikino and co-workers.[65] As outlined in Scheme 3, the required tricyclic skeleton was again effected by the rearrangement of β-patchoulene oxide (**12**).

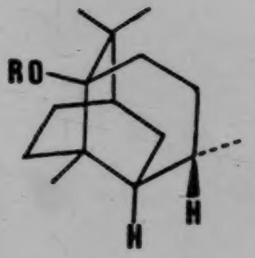
In another synthesis of α-patchoulenone (**6**),[69] an intramolecular addition of diazoketone to olefin (**16**→**17**) served as a key step. Subsequent modification of compound **17** in accordance with the synthetic sequence summarized in Scheme 4 gave the natural ketone in racemic form.

Several years ago, the triketone **18** was prepared in optically active form in our laboratory from ℓ-(−)-camphorsulfonic acid in connection with a project directed towards the total synthesis of α-cedrene (**13**).[70] The intended approach called for an aldol reaction (**18**→**19**) followed by an intramolecular Michael addition (**19**→**20**) to facilitate the construction of the cedrane ring system. During the course of these studies, it was recognized that a reversed sequence of reactions (i.e., Michael reaction and then Aldol condensation), when applied to the analogous trione **21**, could in principle result, *via* the intermediacy of bicyclic trione **22**, in the formation of tricyclic compound **23** possessing the complete carbon framework of α-patchoulene (**1**). Based on this strategy, denominated the Michael-Aldol approach, the synthetic project described in this chapter was initiated. During the course of the investigation, a second approach, designated as the rearrangement approach, emerged. In this approach, the rearrangement of keto epoxide **24** to diketone **25** was involved as a means for the construction of the bridged bicyclic system present in the target molecule.



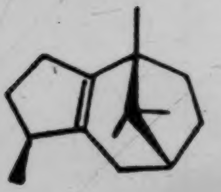
1



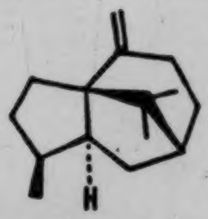


2 = H

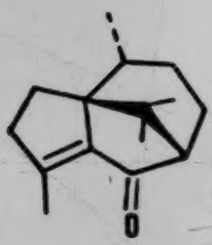
3 = $COCH_3$



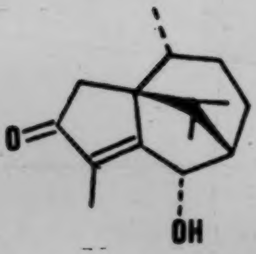
4



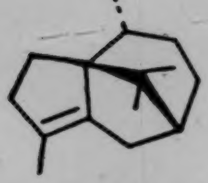
5



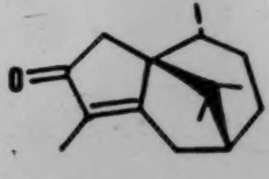
6



7

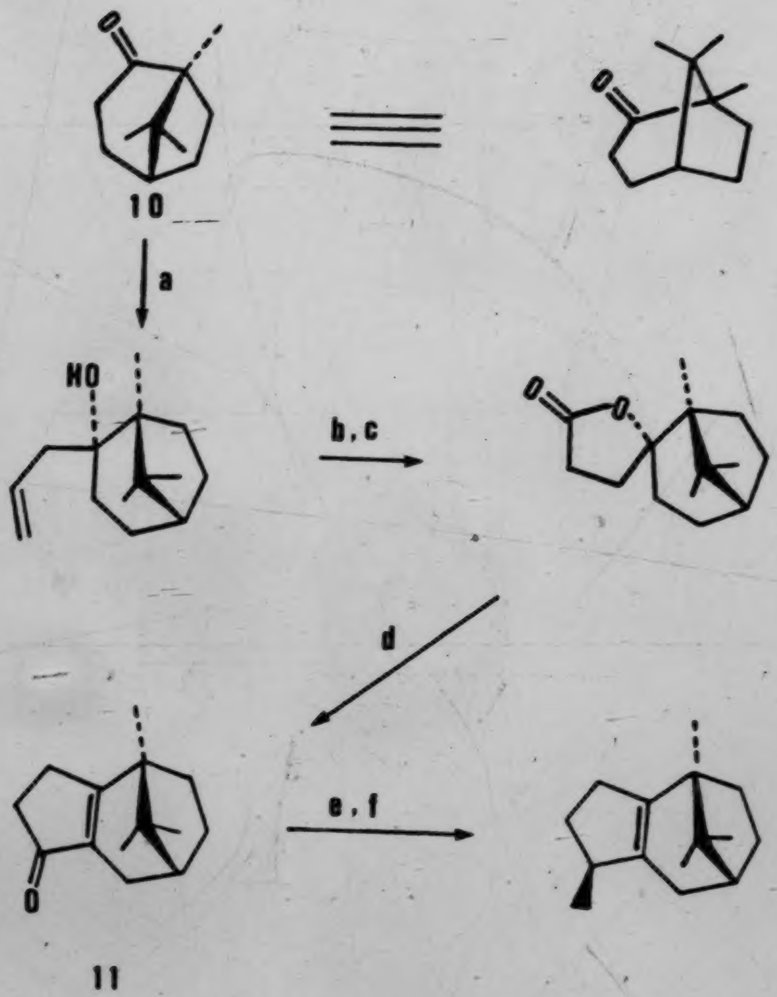


8



9

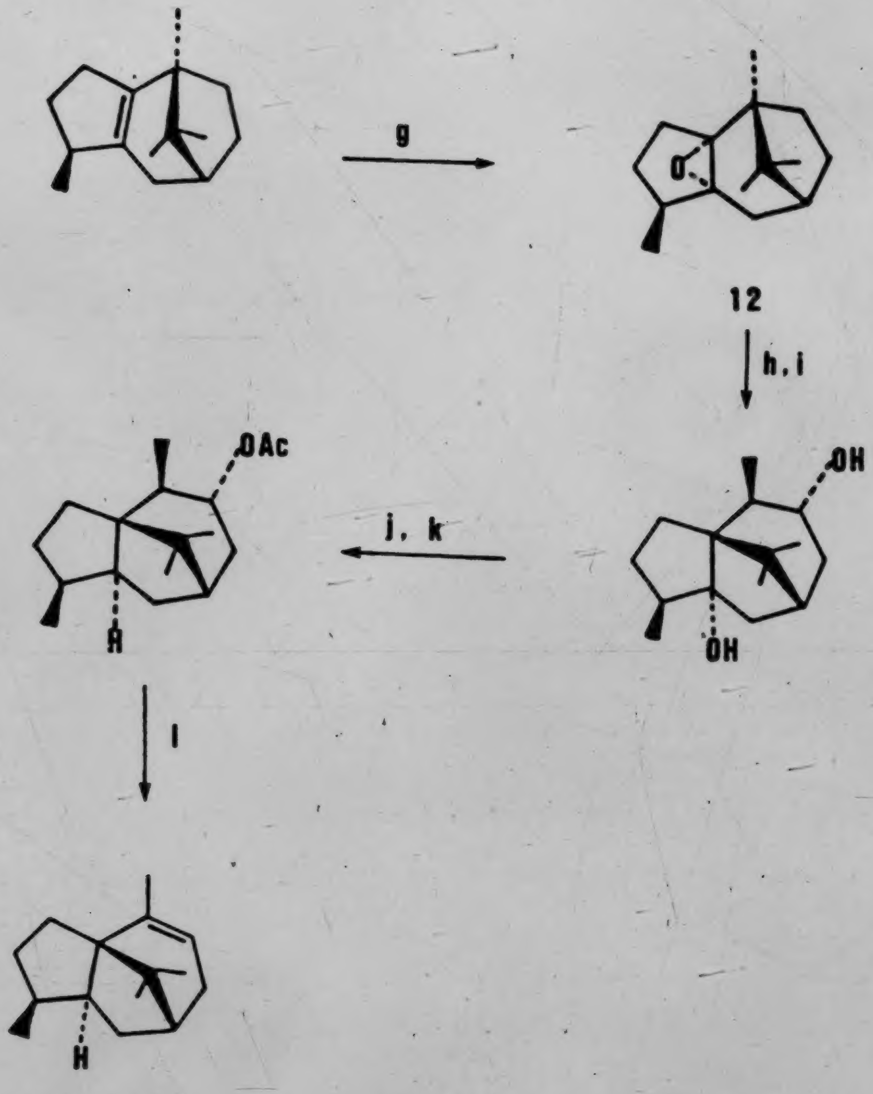
SCHEME 1


10
a
HO
b, c
d
11
e, f

(a)allylmagnesium bromide;(b)$(BH_3)_2$;(c)H_2CrO_4;(d)$ZnCl_2$; HoAc,$(AcO)_2O$;(e)Ph_3PCH_2;(f)Raney nickel W-2;

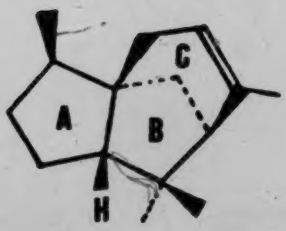
continued...

SCHEME 1 (continued)

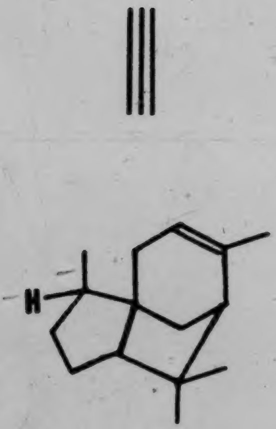

g
O
12
h, i
OH
OH
j, k
OAc
H
l
H

1

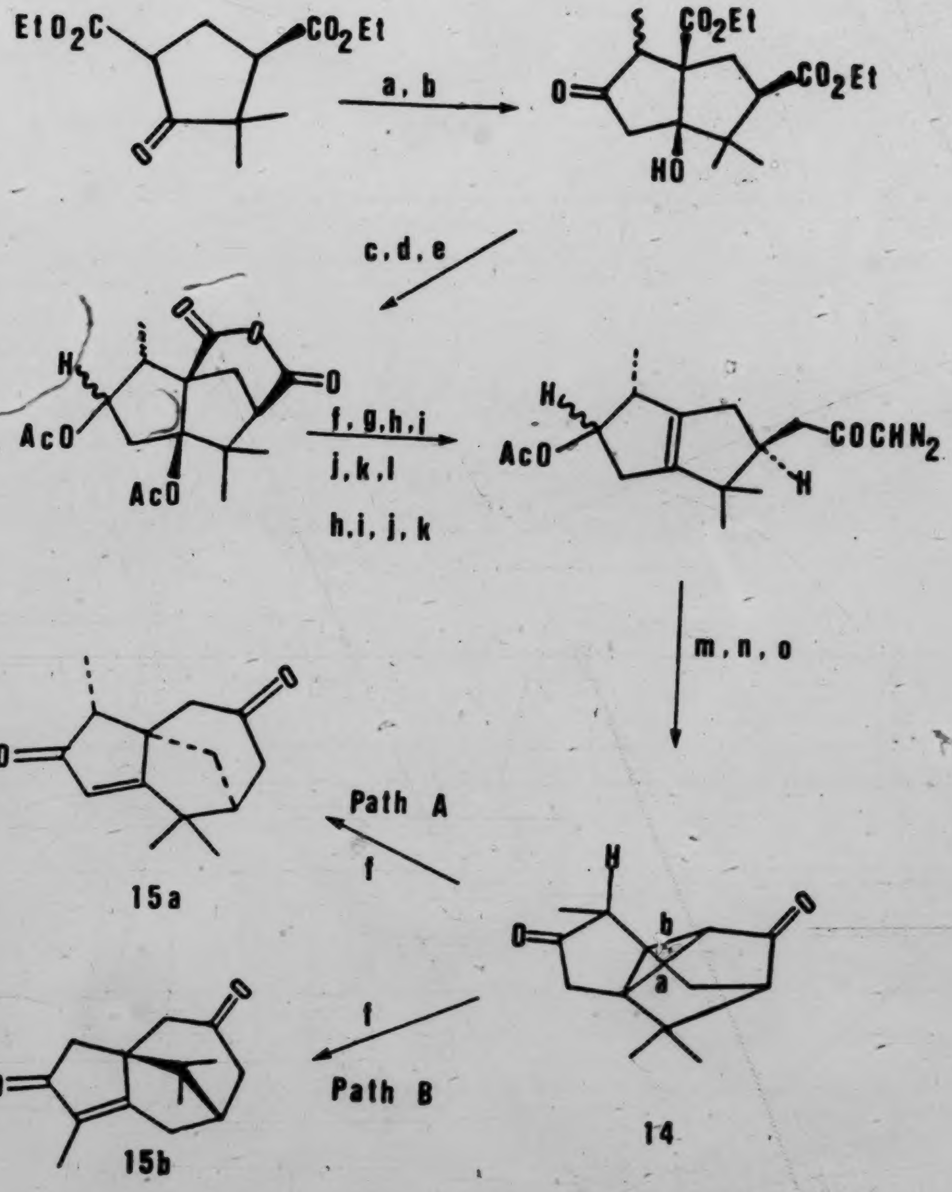
(g)CH_3CO_3OH,NaOAc;(h)$BF_3\cdot Et_2O$;(i)$(BH_3)_2$/ H_2O_2,NaOH;
(j)Ac_2O,Pyr.;(k)PtO_2,H_2,AcOH;(l)350°C.



13

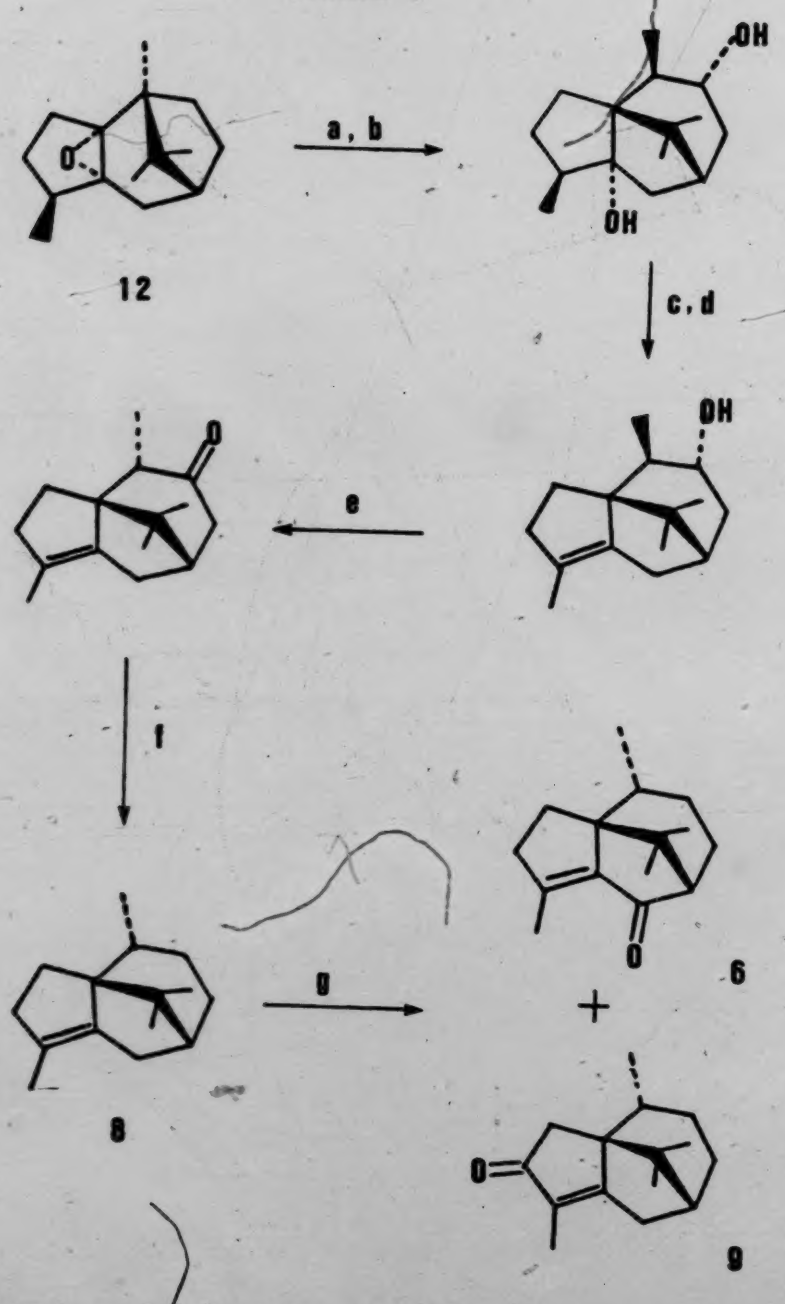


SCHEME 2


EtO2C
CO2Et
a, b
CO2Et
O
CO2Et
HO
c, d, e
H
AcO
AcO
O
f, g, h, i
j, k, l
h, i, j, k
H
AcO
COCHN2
H
m, n, o
O
O
Path A
f
15a
H
O
b
a
O
f
Path B
O
O
15b
14

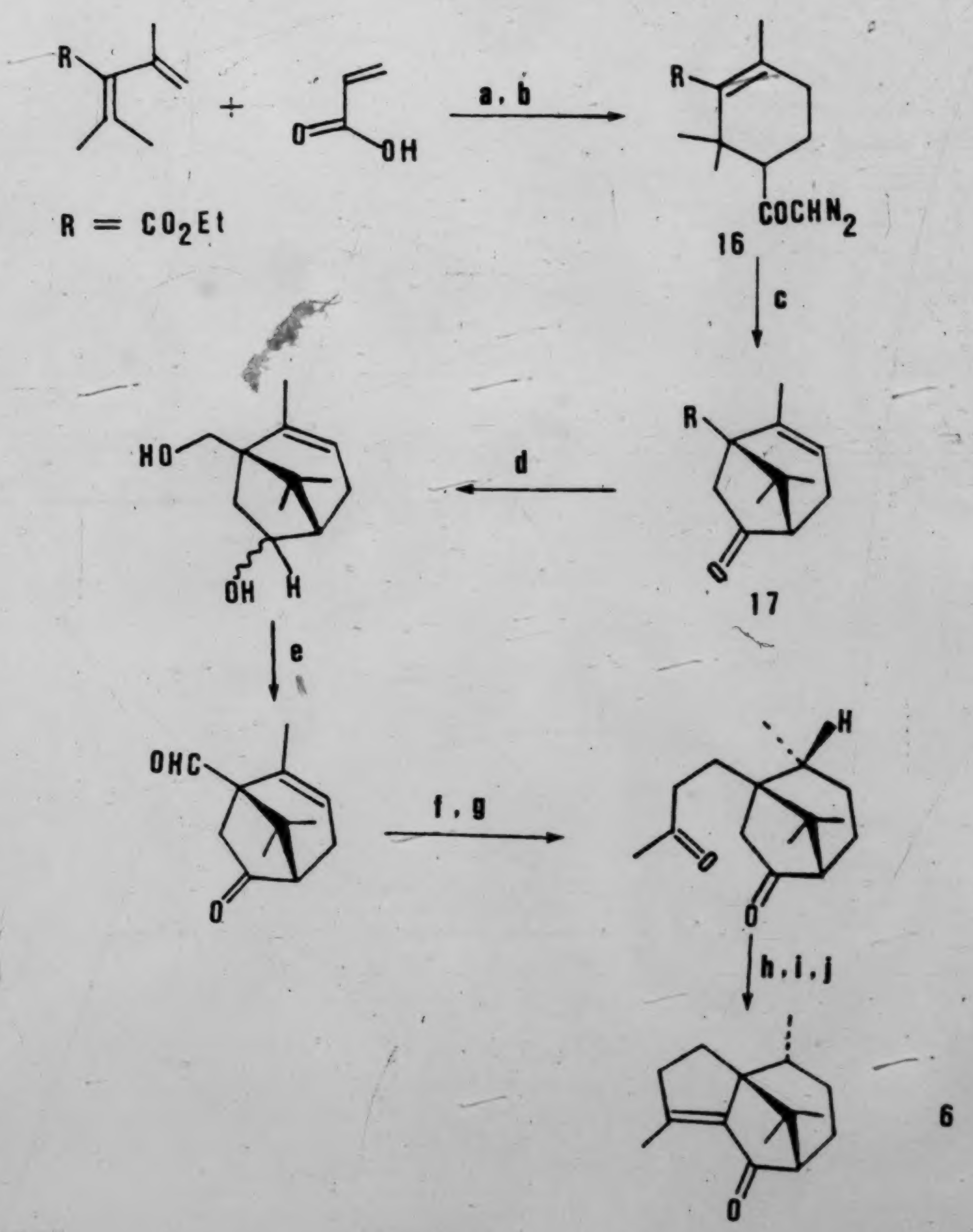
(a)LiH,DME;3-bromo-2-butanone;(b)t-BuOK,t-BuOH;(c)NaBH$_4$, EtOH;(d)KOH,H$_2$O;(e)(CH$_3$CO)$_2$O,p-toluenesulfonic acid; (f)CH$_3$ONa,CH$_3$OH;(g)pyrolysis,200-210°C;(h)NaOH,H$_2$O; (i)(CH$_3$CO)$_2$O,pyridine;(j)oxalyl chloride, pyridine,benzene;(k)CH$_2$N$_2$,ether;(l)Ag$_2$O,CH$_3$OH; (m)copper,benzene,$h\nu$;(n)NaOH,H$_2$O,THF;(o)Pyr$_2$·CrO$_3$.

SCHEME 3

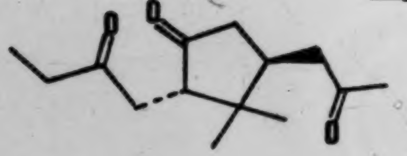

a, b
OH
O
OH
12
c, d
O
e
OH
f
O
6
+
8
g
O
9

(a)$BF_3\cdot Et_2O$;(b)$(BH_3)_2$/ H_2O_2,NaOH;(c)Ac_2O,Pyr.;(d)$LiAlH_4$/ H_2O;(e)H_2CrO_4;(f)NH_2NH_2,KOH,trietylene glycol;(g)t-butyl chromate.

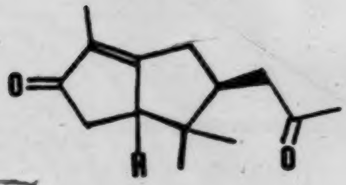
SCHEME 4


R
O
OH
a, b
R
COCHN2
R = CO2Et
16
c
HO
OH
H
d
R
O
17
e
OHC
O
f, g
H
O
O
h, i, j
O
6

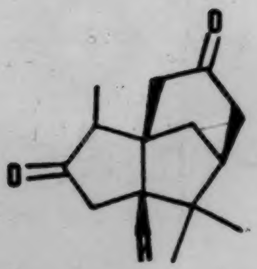
(a)200°c,2000psi;(b)$(COCl)_2$/ CH_2N_2;(c)$BF_3\cdot Et_2O$;(d)$LiAlH_4$;
(e)$Pyr_2\cdot CrO_3$;(f)$(EtO)_2POCH^{\ominus}CO_2Et$ $Na^{\oplus}$,benzene,reflux;
(g)W-5 Raney-nickel;(h)MeLi;(i)H_2CrO_4;(j)t-BuOK,t-BuOH.



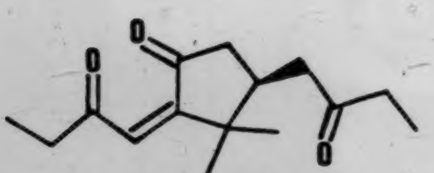
18



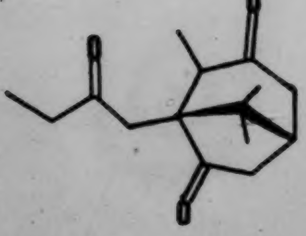
19



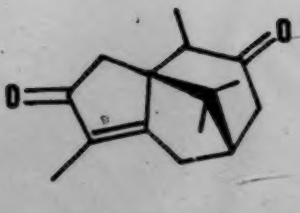
20



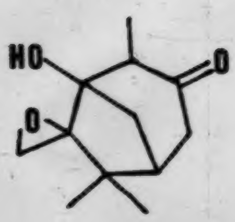
21



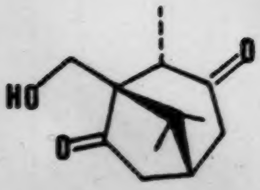
22



23



24



25

RESULTS AND DISCUSSION

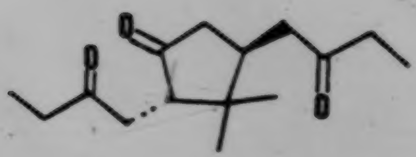
A. Michael-Aldol Approach

As discussed previously, the complete carbon framework of α-patchoulene (**1**) could, in principle, be constructed from enetrione **21** by two consecutive cyclizations, an intramolecular Michael addition followed by the aldol condensation of the resulting bicyclic trione **22** to give enedione **23**. To study this Michael-aldol approach to α-patchoulene, our immediate goal was to prepare the key intermediate **21**. Towards this end, trione **26**, the immediate precursor of **21**, was synthesized as follows _via_ a route analogous to that developed in this laboratory for the preparation of its lower homolog **18**.[70] ℓ-10-Camphorsulfonic acid ammonium salt **27** was heated with fused potassium hydroxide to give (-)-campholenic acid **28** possessing the same chirality as that of α-patchoulene at C-7. Acid **28** was converted to the corresponding ethyl ketone **29** by treatment either with two equivalents of ethyllithium,[71] or sequentially with one equivalent each of lithium hydride and ethyllithium. Ketone **29**, $[\alpha]_D^{23} = -19.04°$ ($c = 1.68$, $CHCl_3$), thus obtained in 92% yield showed an intense carbonyl absorption at 1702 cm^{-1} in the ir spectrum. In the ^{1}Hmr spectrum, three methyl singlets and a methyl triplet appeared at δ 1.61 (broad), 0.99, 0.78 and 1.06 (J = 7 Hz) respectively, while a broad singlet was found at δ 5.21 for the vinylic proton. In agreement with the structural formula of $C_{12}H_{20}O$, the mass spectrum displayed a molecular ion peak at 180.1511.

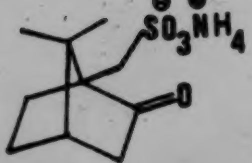
Ketone **29** was subjected to photo-oxygenation[72,73] in methanol using methylene blue as a sensitizer. Reductive work-up of the resulting hydroperoxides with dimethyl sulfide gave rise to a 73% yield of a mixture of two epimeric alcohols **30** in ca. 9:1 ratio as indicated by the ^{1}Hmr spectrum which displayed two sets of signals, each contained two methyl singlets (δ 0.84 and 1.14 for the major, and δ 0.87 and 1.08 for the minor) and a methyl triplet (major at 1.06 and minor at 0.94). The ^{1}Hmr also showed two broad singlets integrating to one proton each at δ 5.17 and 4.98 for the exocyclic methylene protons of both epimers and a broad doublet at δ 4.44 for the proton adjacent to the hydroxyl group for both compounds. The ir and mass spectra were consistent with the structural assignment. The former showed characteristic absorption bands at 3420 and 1702 cm^{-1} for the hydroxyl group and the ketone carbonyl respectively. In the latter spectrum, the required molecular ion peak at 196.1463 was observed.

When the mixture was subjected to column chromatography with extreme care, the major isomer could be obtained in pure form and showed a specific rotation of -42.94° (c = 0.34, $CHCl_3$) at room temperature using the sodium D line. However, since the newly created chiral center would be destroyed in the subsequent transformation, the epimeric mixture could be conveniently used without separation.

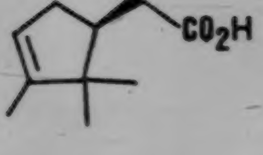
Manganese dioxide[70] and ceric (IV) ammonium nitrate[74] were used in initial attempts to bring about the oxidation of the epimeric alcohols **30** to enone **31**. These reagents proved to be ineffective giving invariably complex mixture of products. Alternatively, the mixture of alcohols **30** was subjected to Moffatt oxidation using Swern's modification.[75] To our delight, the desired enone **31** was formed as a single product in 93% yield, when alcohols **30** were treated sequentially with oxalyl chloride and dimethylsulfoxide in dichloromethane and then with triethylamine over a temperature range of -78°C to 20°C. The ir spectrum of enone **31** showed two carbonyl absorption bands, one at 1728 cm^{-1} (five-membered enone) and the other at 1710 cm^{-1}, as well as a double bond absorption at 1634 cm^{-1}. A molecular ion peak at 194.1306 in the mass spectrum was consistent with the required molecular formula of $C_{12}H_{18}O_2$. In the ^{1}Hmr spectrum, two one-proton singlets at δ 5.95 and 5.18 were observed for the vinylic



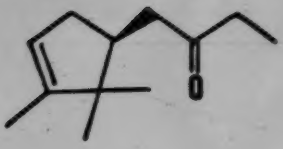
26



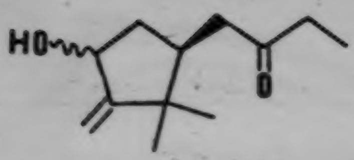
27



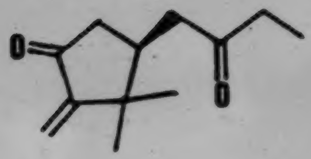
28



29



30



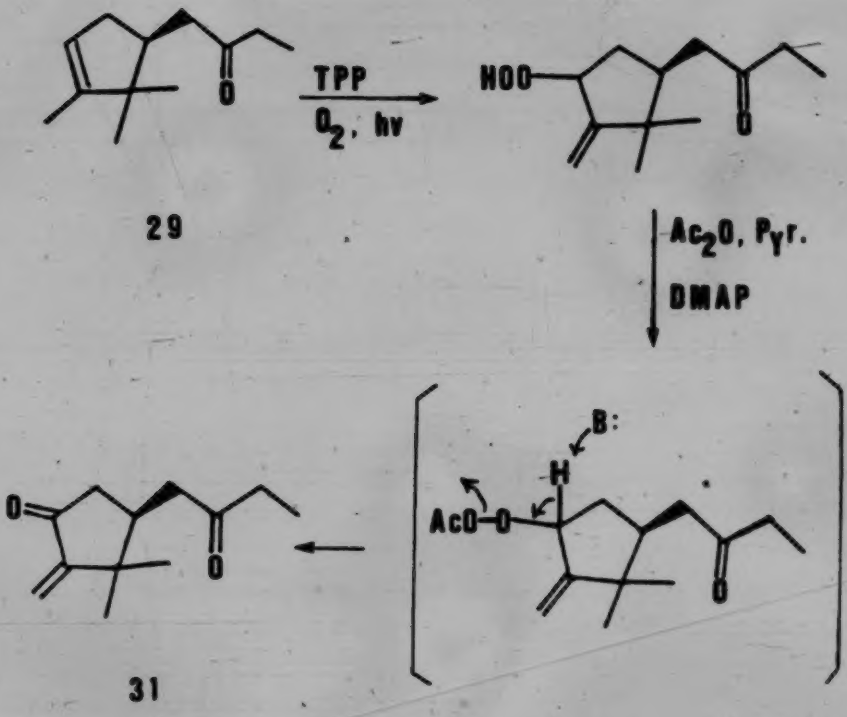
31

protons, along with three methyl signals, a triplet ($J = 8$ Hz) at δ 1.07 and two singlets at δ 1.01 and 1.22.

Enone **31** could also be prepared directly from ketone **29** by carrying out the photo-oxygenation reaction in dichloromethane in the presence of acetic anhydride, pyridine and 4-dimethylaminopyridine using 5,10,15,20-tetraphenyl-21H,23H-porphine (TPP) as a photosensitizer.[76] As depicted in Scheme 5, under these conditions, the initially formed hydroperoxide was acetylated and the resulting peroxyacetate underwent further elimination to give the desired enone **31** in a yield (~60%) comparable to that obtained from the two-step reaction sequence described above. Although shorter in synthetic steps, the direct method was less preferred in practice because of the difficulties encountered to remove TPP. The most effective method to achieve its removal by distillation could not be applied due to the instability observed for enone **31** which underwent substantial decomposition upon heating.

To install the second 2-oxobutyl chain present in trione **22**, enone **31** was treated with 1-nitropropane and potassium carbonate[77] at room temperature in methanol. The Michael addition occurred readily giving rise to, in near-quantitative yield, crystalline nitro ketone **32** (m.p. 82-83°C) which showed, in the ir spectrum, a strong

SCHEME 5

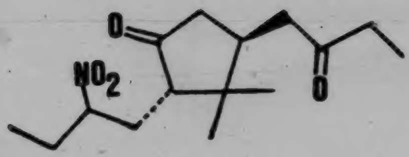

TPP
O_2, hv
HOO
Ac_2O, Pyr.
DMAP
B:
H
AcO–O
O
O

29

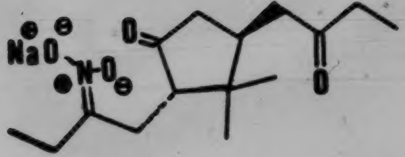
31

absorption at 1542 cm^{-1} characteristic of the nitro group and two carbonyl bands at 1732 and 1708 cm^{-1}. The ^{1}Hmr spectrum displaced two methyl singlets at δ 0.64 and 1.06 and two methyl triplets (J = 8 Hz each) centered at δ 0.89 and 0.98. The observed sharp melting point coupled with the simplicity of the ^{1}Hmr spectrum suggested that a single stereoisomer of nitro ketone **32** was produced. Since the applied conditions are expected to give the thermodynamically more stable product, its stereochemistry was tentatively assigned as depicted in the formula.

Nitro ketone **32** was treated with a slight excess of sodium methoxide in methanol and the corresponding sodium salt **33** thus formed was subjected to ozonolysis at -78°C. Reductive work-up with dimethyl sulfide gave rise to trione **26** (87% yield) in crystalline form, m.p. 68-69°C. The structure of trione **26** was readily established on the basis of the following spectral data. In the ir spectrum, diagnostic ketone carbonyl absorption bands were observed at 1736 and 1708 cm^{-1} while a molecular ion peak at 252.1728 was displayed in the mass spectrum in agreement with the molecular formula of $C_{15}H_{24}O_3$. The ^{1}Hmr spectrum indicated the presence of a total of four methyl groups showing two singlets at δ 0.65 and 1.05 and two triplets at δ 0.98 and 1.16, each with a coupling constant of 8 Hz.



32

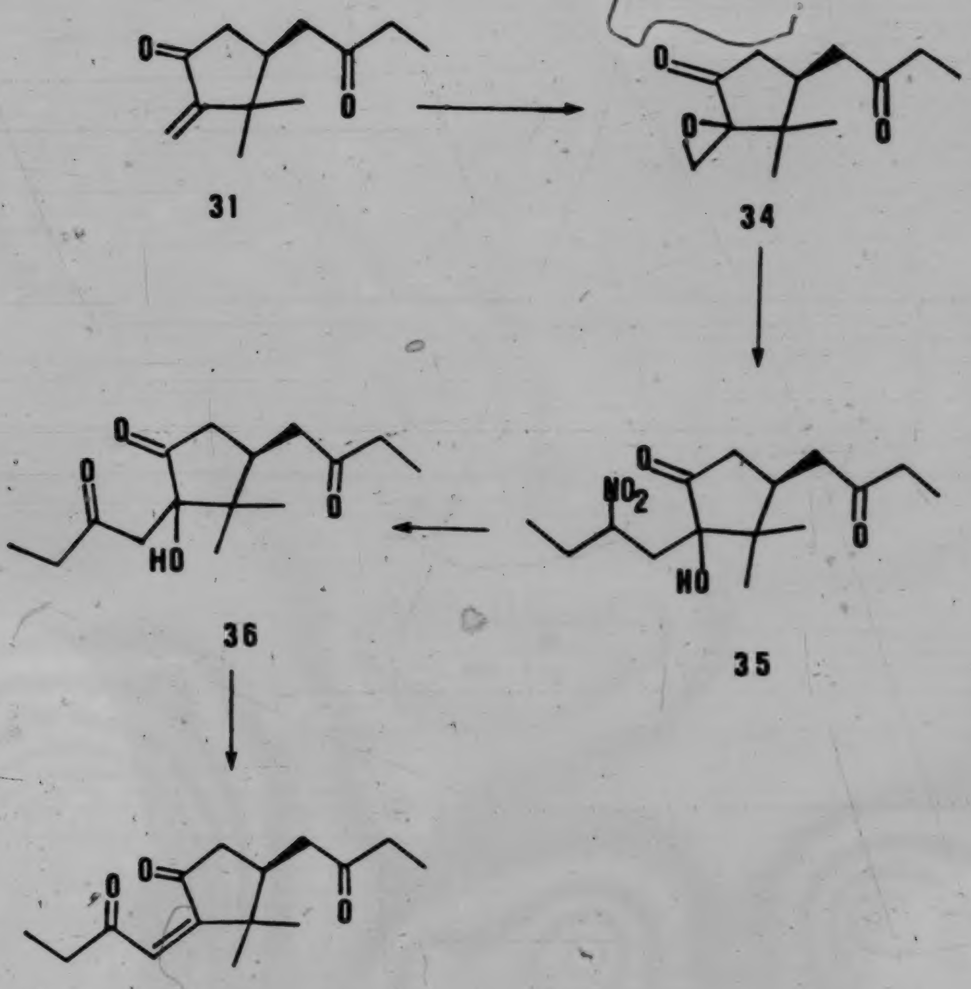


33

The preparation of enetrione **21**, the key intermediate in the Michael-Aldol approach according to the synthetic plan, from trione **26** requires the introduction of a double bond to the 1,4-dione moiety of the latter compound. Several reagents such as dichlorodicyanoquinone[78,79] and selenium dioxide[80] are known to effect directly this type of transformation. These reagents were applied. The results were, however, very disappointing. Under a variety of conditions, the attempted reactions resulted in either the recovery of the starting material or the formation of complex mixtures. In no case was the desired product detected. Equally disappointing were the results obtained from the attempted indirect oxidation reactions via halogenation[81] and phenylselenenylation.[82] Invariably, a mixture of a large number of unidentified products was formed. As a consequence of these negative findings, an alternative route leading to enetrione **21** was sought.

It is conceivable that epoxide **34** could undergo substitution reaction with a suitable nucleophile such as nitropropane (**34**→**35**) and the resulting alcohol **35** could eventually provide the double bond in question by dehydration (**36**→**21**) (Scheme 6). Towards this end, enone **31** was subjected to epoxidation using 30% hydrogen peroxide and sodium hydroxide in methanol.[83] A

SCHEME 6



31

34

35

36

21

crystalline compound (m.p. 95-96°C) was produced in 25% yield. This compound was shown spectroscopically to be not the epoxide **34** but alcohol **37** resulting from an intramolecular aldol reaction. Its molecular composition of $C_{12}H_{18}O_2$ was verified by the mass spectrum which displayed a molecular ion peak at 194.1306. The ir spectrum indicated the presence of hydroxy group (3445 cm^{-1}), saturated six-membered ring ketone (1702 cm^{-1}) and carbon-carbon double band (1655 cm^{-1}). In the ^{1}Hmr spectrum, vinylic protons were observed at δ 5.00 and 4.96, each as a singlet integrating to one hydrogen atom. The spectrum also showed three methyl signals, one doublet at δ 1.02 with a coupling constant of 7 Hz and two singlets at δ 0.94 and 1.12. As suggested by its melting point and ^{1}Hmr spectrum, alcohol **37** was most likely formed as a single stereoisomer. An examination of the Dreiding models reveals that, of the two possible epimers, the one with an exo-orientated methyl group is considerably less congested sterically. Hence, under equilibrium conditions, this compound could be produced preferentially. It was based on these considerations that the stereochemistry of alcohol **37** was tentatively assigned.

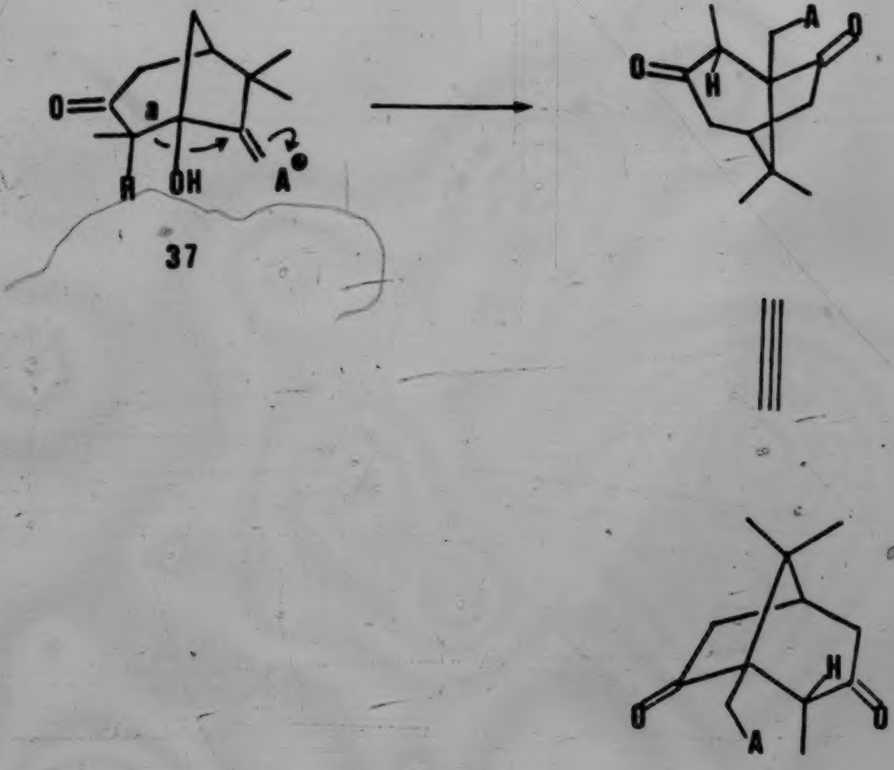
The formation of alcohol **37** suggested an interesting and remarkably simple solution to the problem of constructing the B/C ring system of α-patchoulene (**1**). It was realized that alcohol could, in principle, be transformed to the required bridged bicyclic system via a Wagner-Meerwein rearrangement^{84} involving the migration of the strategic bond a as depicted in Scheme 7. Since both the hydroxyl group and the ketone carbonyl are expected to provide additional driving force, the desired bond migration should proceed with ease and high selectivity.

The lack of success in securing enetrione **21** required for the Michael-Aldol approach to α-patchoulene necessitated a redirection of the synthetic strategy. At the same time, the rearrangement reaction presented itself as a highly attractive pathway leading to the synthetically demanding bridged ring system of the target molecule. As a consequence of these events, further studies were centered at the rearrangement approach. Results are described in the following section.

B. The Rearrangement Approach

In order to make use of this approach effectively, a fundamental problem of immediate concern was the improvement of the aldol reaction of **31** leading to the formation of hydroxy ketone **37**. The aldol reaction is known to be reversible. In the present case, the situation is further complicated by the presence, in the molecule, of

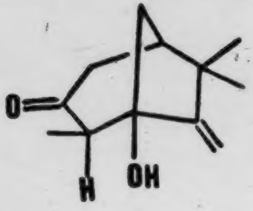
SCHEME 7


O
a
R
OH
A⊕
O
H
A
O
H
A
O
O

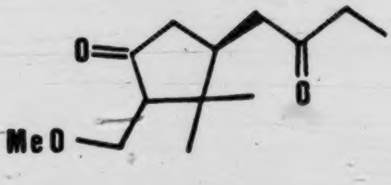
37

38

an α,β-unsaturated ketone moiety which can easily undergo Michael reaction (also reversible) with external nucleophiles. In order to suppress these undesirable competing reactions, an extensive search of a favorable combination of solvent and base was carried out. Solvents examined include methanol, ethanol, 2-propanol, t-butyl alcohol, 1,2-dimethoxyethane, tetrahydrofuran, and benzene, while pyridine, triethylamine, diisopropylamine, sodium carbonate, potassium carbonate, sodium bicarbonate, sodium methoxide, sodium t-butoxide, and sodium hydride were explored as potential bases. Unfortunately, an ideal set of conditions, which would induce exclusively the desired reaction, could not be reached. The best results were obtained when the reaction was carried out in methanol at room temperature using sodium carbonate or potassium carbonate as a base. Under these conditions, the desired product **37** was formed preferentially (two parts) along with the Michael adduct **39** (one part), while the starting material was recovered to the extent of 25%. Fortunately, the total material recovery was excellent, virtually without any loss of material. By recycling once the mixture of adduct **39** and the starting material recovered, which was separated from hydroxy ketone **37** by column chromatography, the desired compound could be obtained in a total yield of 75%. The structure



37

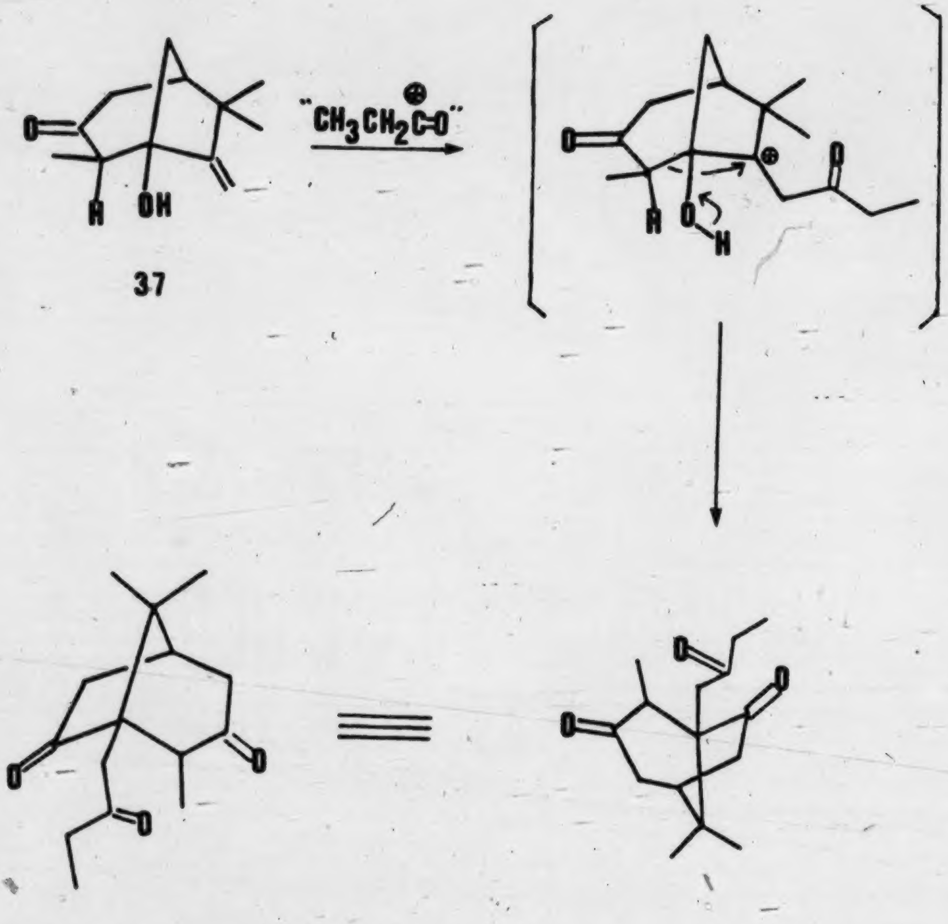


39

of the Michael adduct **39** follows clearly from its spectral data. The ^{1}Hmr spectrum showed a methoxy singlet at δ 3.52 and a multiplet at δ 3.50 for the methylene protons adjacent to the methoxy group. The methyl groups were found to resonate at δ 1.08, 0.75 and 1.22, the former as a triplet and the latter two as singlets. In the ir spectrum, two carbonyl absorption bands were observed, one at 1736 cm^{-1} characteristic of a saturated five-membered ketone and the other at 1706 cm^{-1} for the butanone moiety. In further support of the structural assignment, the mass spectrum displayed a molecular ion peak at 226.1561 indicating a molecular composition of $C_{13}H_{22}O_3$.

Although, on treatment with a Lowry-Brønsted acid or a commonly used Lewis acid, hydroxy ketone **37** is expected to undergo Wagner-Meerwein rearrangement with the desired migratory aptitude, such a process is virtually useless for the present synthetic purpose. This is immediately apparent, since the anticipated product **38** could not be easily elaborated further due to the lack of functionality on the substituent attached to the bridge-head carbon. It is thus clear that the rearrangement reaction alone is not synthetically useful unless a functionalized side-chain can be introduced to the bridged-head carbon simultaneously. An exceedingly interesting possibility was the use of an acylium ion to trigger the Wagner-Meerwein rearrangement. As shown in Scheme 8, by such a process, a highly useful ketonic side-chain could be incorporated to the molecule at a strategic point. Moreover, when a propionyl acylium ion is used, the anticipated product **22** could, in principle, be subsequently cyclized by an aldol process to provide the complete carbon skeleton of the target molecule (**1**). Both aromatic (Friedel-Crafts acylation[85]) and aliphatic carbon-carbon double bonds[86,87] are well known to undergo addition reactions with acylium ions which are usually generated in situ from an active acid derivative (e.g. acid chloride) and a Lewis acid. Accordingly, hydroxy ketone **37** was subjected to "Friedel-Crafts reaction" with propionylium ion preformed using propionyl chloride and stannic chloride at 0°C in carbon disulfide. However, hydroxy ketone **37** was found to be unreactive under these conditions even after a prolonged period of time. On the other hand, when the reaction was carried out in chloroform at room temperature, a compound was produced in 90% yield. This compound was shown to possess the molecular formula of $C_{15}H_{22}O_3$ in agreement with the desired product **22** by the mass spectrum which displayed a molecular ion peak at 250.1569. However, the ir spectrum showed, in addition to carbonyl absorptions at 1750 and 1734 cm^{-1}, a band at 1686 cm^{-1} suggesting the presence of a carbon-carbon double bond or an α,β-

SCHEME 8


"CH₃CH₂C≡O⁺"
O
H
OH
O
H
O

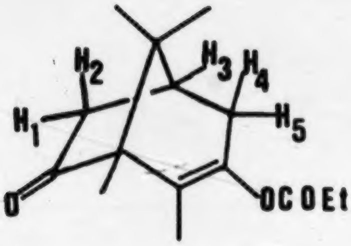
37

22

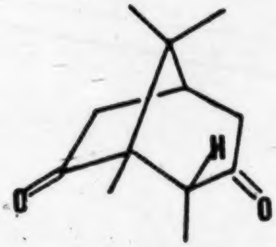
unsaturated ketone moiety, neither of which could be accounted for by the structure of the desired compound **22.** It was further disclosed by a careful ^{1}Hmr analysis that the product was in fact not the desired **22** but the isomeric enol propionate **40.** A total of five methyl signals were apparent, three as singlets at δ 1.06, 1.03 and 0.85, one at 1.43 (vinylic methyl) as a triplet with a small allylic coupling constant of 2 Hz, and the remaining signal at 1.17 also as a triplet which was found to mutually couple with a methylene quartet at δ 2.43. With the aid of decoupling experiments, the remaining protons of **40** could also be conclusively determined as follows. The bridge-head proton H_3 appeared at δ 1.98 as a doublet of doublets of doublets with three vicinal coupling constants of 7 (H_{3-4}), 4 (H_{3-2}), and 2 Hz (H_{3-1}). Protons H_4 and H_5, which were found to resonate at δ 2.53 and 2.22 respectively, coupled to each other with a large geminal coupling constant of 19 Hz. The former was further coupled with H_3 (7 Hz), whereas H_3-H_5 coupling was not observed. Protons H_1 (δ 1.91) and H_2 (δ 2.70) were found also to couple to each other with a large geminal coupling constant of 17 Hz. In addition, each of these protons was coupled with the bridge-head proton H_3 (*vide supra*) and with the vinylic methyl group with a small coupling constant of 2 Hz.

To confirm the structural assignment, enol propionate **40** was subjected to treatment with sodium methoxide in methanol. Diketone **41** thus obtained in quantitative yield showed, in its ir spectrum, two carbonyl absorption bands, one at 1738 cm^{-1} for the five-membered ring ketone and the other at 1702 cm^{-1} for the six-membered ring ketone. A molecular ion peak was displayed at 194.1302 in the mass spectrum in agreement with the required molecular formula of $C_{12}H_{18}O_2$. The ^{1}Hmr spectrum showed a doublet at δ 0.98 with a coupling constant of 7 Hz and three singlets at δ 0.97, 0.99 and 1.23 for a total of four methyl groups. The fact that only one set of methyl signals were observed further suggested that a single stereoisomer was produced. On the basis of thermodynamic stability, the stereochemistry was tentatively assigned as depicted.

Several other Lewis acids were employed in attempts to effect the transformation **37**→**22**. However, the use of boron trifluoride etherate, zinc chloride, and aluminum chloride all failed to change the course of the reaction. In all cases examined, enol propionate **40** was formed as the sole product without exception. The only major differences observed were the rate of reaction and the yield of product. Aluminum chloride was shown to be the most powerful catalyst. With this catalyst, the reaction proceeded more rapidly (1.5 h) than that with stannic


H2
H3
H4
H1
H5
O
OCOEt

40



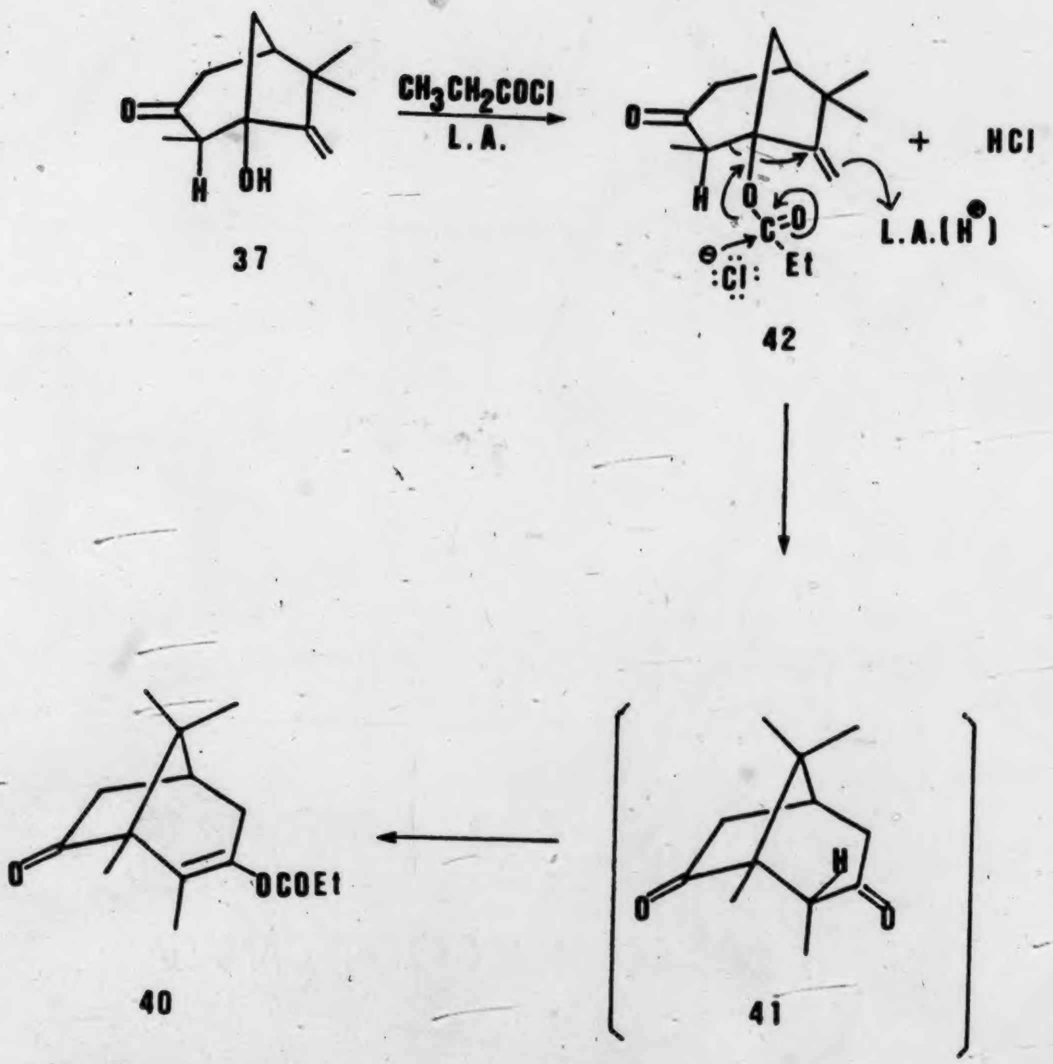
41

chloride but the yield (75%) of product **40** was somewhat poorer. Zinc chloride was less effective than stannic chloride both in terms of reaction rate (24 h for zinc chloride) and product yield (~70%). With boron trifluoride etherate, the reaction proceeded rather slowly; only 20% conversion was observed after 24 h. During the course of these studies the following observation was also made. When keto alcohol **37** was exposed briefly (45 min) to propionyl chloride in methylene chloride at 0°C in the presence of stannic chloride or aluminum chloride, the corresponding propionate **42** was formed in 95% yield. This compound, which could be independently formed by acylation of **37** with propionyl chloride and pyridine in ether, showed, in the ir spectrum, an ester carbonyl absorption band at 1731 cm^{-1}, a characteristic ketone carbonyl absorption band at 1708 cm^{-1} and also a weak absorption band at 1652 cm^{-1} for carbon-carbon double bond. A molecular ion peak was found at 250.1567 in the mass spectrum in agreement with the required molecular formula of $C_{15}H_{22}O_3$. The ^{1}Hmr spectrum showed a singlet at δ 5.01 for two vinylic protons. A total of four methyl groups was found at δ 1.23, 0.99 (singlets), 1.60 (a triplet with a coupling constant of 7.5 Hz), and 0.96 (a doublet with a coupling constant of

7 Hz). The stereochemistry was tentatively assigned as depicted on the basis of thermodynamic stability.

The isolation of propionate **42** and the outmost formation of enol propionate **40** in the Lewis acid catalyzed reaction of keto alcohol **37** with propionyl chloride strongly suggested that the reaction proceeded via the mechanistic pathway outlined in Scheme 9. Keto alcohol **37** was first esterified under acid catalysis to give the corresponding propionate **42** which underwent subsequent rearrangement to give the diketone **41**. Esterification of **41** eventually resulted in the formation of enol propionate **40**. An analysis of the hypothetical reaction pathway raised an interesting question. Since hydrogen chloride was formed as a by-product in the initiating step, it is conceivable that the undesired rearrangement reaction leading ultimately to enol propionate **40** could have been induced by it. In the absence of hydrogen chloride, propionate **42** might well undergo the "Friedel-Crafts reaction" giving rise to the desired product **22**. With this in mind, pure propionate **42** was subjected to treatment with propionyl chloride and stannic chloride in methylene chloride at 0°C. Unfortunately, the prediction proved to be incorrect and enol propionate was again produced in a high yield of ~90%. Similar results were also obtained using aluminum

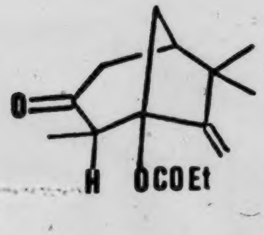
SCHEME 9


O
H
OH
37
CH_3CH_2COCl
L.A.
O
H
O
C
O
Et
:Cl:
42
+ HCl
L.A.(H$^{\oplus}$)
O
H
O
41
O
OCOEt
40

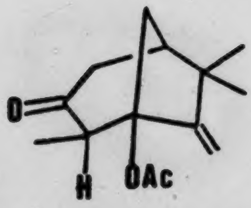
chloride as a catalyst or the combination of zinc chloride and propionic anhydride.[86]

The "Friedel-Crafts" reaction was also attempted on acetate **43** which was readily prepared by treatment of keto alcohol **37** with acetyl chloride and pyridine. It was considered that the presence of a large propionate substituent in compound **42** could hamper the desired reactivity of the double bond towards propionylium ion. The situation could be somewhat rectified by using the smaller acetoxy group. Thus, acetate was treated with zinc chloride and propionic anhydride. Disappointingly, the undesired enol propionate **40** was again obtained as the sole product in near-quantitative yield regardless of the reaction conditions (0°C or refluxing in methylene chloride).

An intramolecular "Friedel-Crafts" process was also examined with the intention of preparing an oxalic acid derivative **44**. On exposure to a suitable Lewis acid, this compound could, in principle, proceed via the "Friedel-Crafts" reaction in an intramolecular fashion to give compound **44** as outlined in Scheme 10. Towards this end, hydroxy ketone **37** was treated with oxalyl chloride and stannic chloride at 0°C for 24 h. Unexpectedly, under these conditions, keto alcohol **37** underwent a retro-aldol reaction giving rise to enone **31** as the major product. In

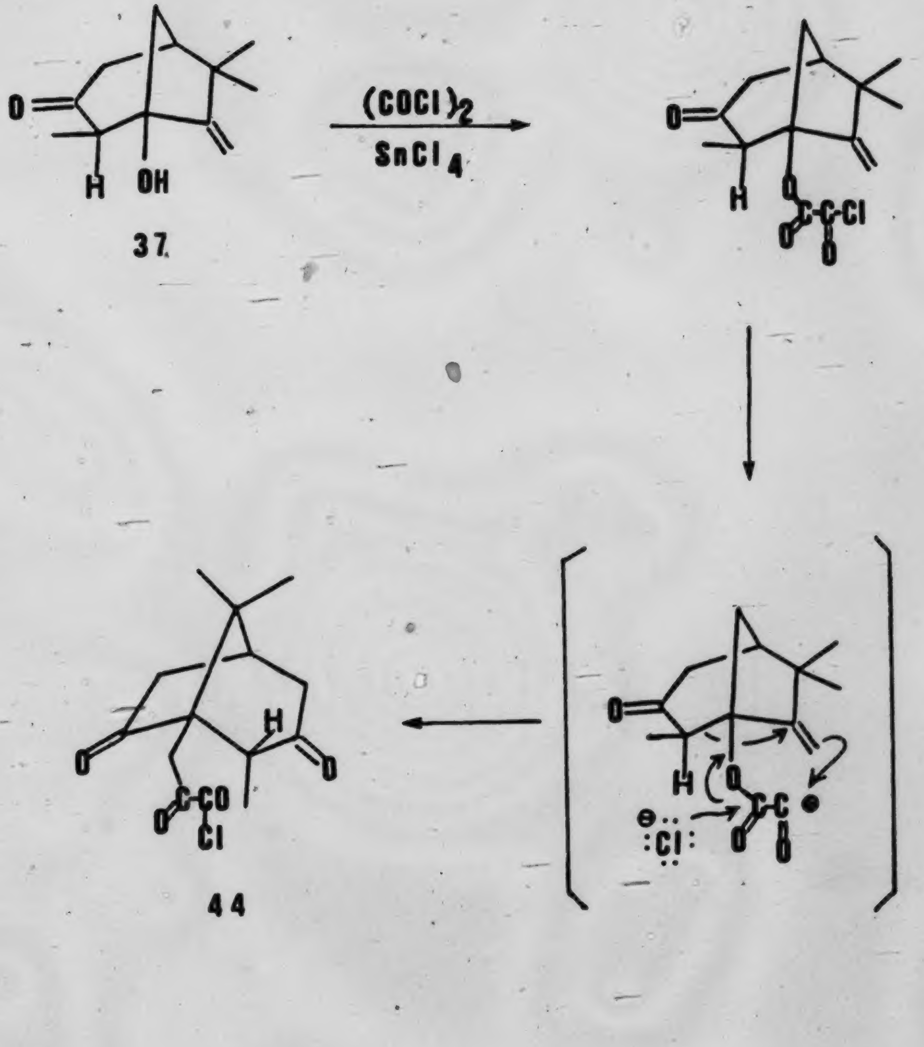


42



43

SCHEME 10

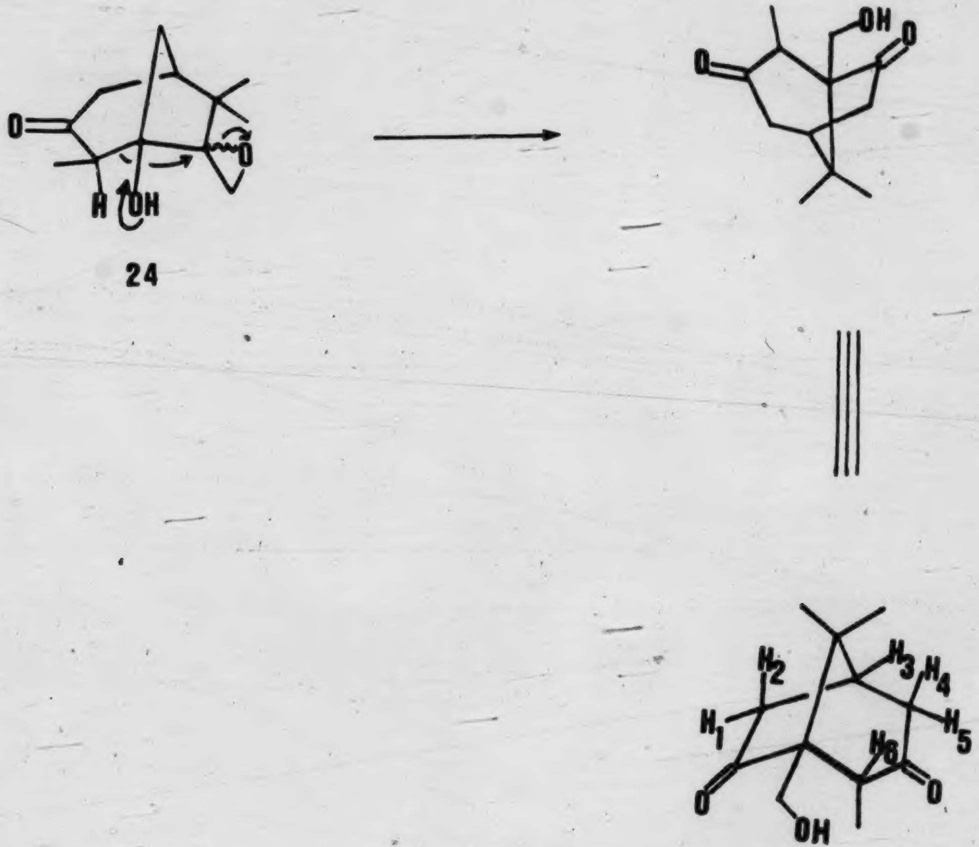

O
H
OH
37
(COCl)$_2$
SnCl$_4$
O
H
O
C-C-Cl
O
O
O
H
O
C-C
O
O
⊖
:Cl:
⊕
O
H
O
C-CO
O
Cl
44

another experiment a complex mixture was formed when keto alcohol **37** was treated with pyridine and oxalyl chloride in methylene chloride at 0°C for 5 min followed by the addition of stannic chloride and allowing the mixture to react at room temperature for 20 h.

The above experiments were so designed that the Wagner-Meerwein rearrangement of keto alcohol **37** could be effected with concomitant incorporation of a suitably functionalized three-carbon unit to the molecule at a strategic position. After a long search for appropriate reaction conditions without success, it was deemed necessary to modify the synthetic plan. As noted previously the Wagner-Meerwein rearrangement will not be synthetically useful unless the bridge-head substituent of the product could be simultaneously functionalized. In approaches to this problem, epoxide **24** represents itself as an attractive alternative candidate to fulfill the requirements. This compound is expected to undergo facile rearrangement (Scheme 11) under acid catalysis to give hydroxy dione **25** possessing not only the B/C ring system of the target molecule (**1**) but a hydroxymethylene group on the bridge-head carbon suitable for further manipulation.

Towards the preparation of epoxide **24**,[88] keto alcohol **37** was treated with m-chloroperbenzoic acid in methylene chloride at room temperature. After 3 h, the reaction was

SCHEME 11


O
H
OH
O
OH
O
O
H2
H3
H4
H1
H5
H6
O
O
OH

24

25

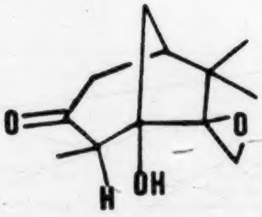
shown to be complete and a mixture of two epimeric epoxides **24** in ca. 3:2 ratio was isolated in a total yield of 85%. The mixture showed a hydroxyl absorption at 3494 cm^{-1} and a ketone carbonyl absorption at 1704 cm^{-1} in the ir spectrum and a molecular ion peak at 210.1264 in the mass spectrum. The ^{1}Hmr spectrum showed two one-proton doublets at δ 2.93 and 2.81, each with a coupling constant of 4 Hz, for the methylene group attached directly to the oxygen atom and the absence of any vinylic protons. In addition, two sets of methyl signals in a ratio of ca. 3:2 were observed indicating the presence of two diastereomers. For the major isomer, the signals appeared at δ 0.9 and 1.02, each as a singlet, and at δ 1.28 as a doublet with a coupling constant of 7 Hz, while the minor set consisted of a doublet (J = 7 Hz) at δ 1.11 and two singlets at δ 0.89 and 0.96.

When the epoxidation reaction of keto alcohol **37** was performed for an extended period of 16 h, two crystalline compounds were formed in a ratio of 3:2. The minor product, m.p. 117-118°C, was found to be identical by ^{1}Hmr analysis with the minor epoxy ketone obtained previously. The major product (m.p. 96-97°C), which was found to be a new compound, showed, in the ir spectrum, a hydroxy absorption band at 3495 cm^{-1} and two carbonyl absorptions at 1732 and 1703 cm^{-1} characteristic of five-membered and six-membered ring ketones respectively. The molecular formula of $C_{12}H_{18}O_3$ as determined by the mass spectrum indicated that it was an isomer of epoxy ketone **24**. These spectral evidences coupled with the mechanistic considerations (Scheme 11) suggested that the compound was the desired rearrangement product **25**. The structure was confirmed by the ^{1}Hmr spectrum which displayed two methyl singlets at δ 1.16 and 1.43 as well as a methyl doublet ($J = 7$ Hz) at δ 1.08. The latter signal was found to mutually couple with the quartet at δ 3.01 which was attributed to H_6. The presence of the hydroxymethylene unit was evident from the doublets at δ 3.93 and 3.84, which were shown to couple with each other with a large geminal coupling constant of 11 Hz, and the singlet at δ 1.79 which disappeared on addition of deuterium oxide. Also in agreement with the assigned structure were signals at δ 2.19, a doublet of doublets of doublets with coupling constants of 8, 3.5 and 3 Hz due to H_3, δ 2.60 and 1.96 for the methylene protons H_4 and H_5 respectively, the former as a doublet of doublets of doublets ($H_{4-5} = 19$, $H_{4-3} = 8$, and $H_{4-2} = 3$ Hz) and the latter as a doublet with a geminal coupling constant of 19 Hz. The methylene protons of the six-membered ring ketone appeared at δ 2.38 (H_1) and 2.86 (H_2) coupled to each other with a large coupling constant of 17 Hz. Proton H_2 was further coupled to both H_3 (J = 3.5 Hz) and H_4 (J = 3 Hz) while only one additional coupling was observed for H_1 (J_{1-3} = 3 Hz).

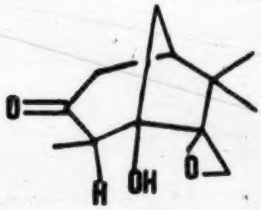
The findings that, under the similar conditions, brief treatment of keto alcohol **37** gave a mixture of two epoxides **24** in ca. 3:2 ratio whereas prolonged treatment resulted in the formation of a single isomer of epoxide **24** and diketone **25** also in 2:3 ratio, suggested that the major isomer initially produced in the epoxidation underwent selectively rearrangement reaction to give diketone **25**. The ease of rearrangement of the major isomer further suggested its structure of **45** (and thus structure **46** for the minor isomer) in which the carbon-oxygen bond and the carbon-carbon bond involved in the rearrangment process are aligned in a favorable anti-parallel manner.

The rearrangement of the minor epoxide **46** could also be effectively carried out, although somewhat more severe conditions were needed. Upon treatment of **46** with stannic chloride[89] at room temperature in chloroform for 8 h, diketone **25** was formed in 92% yield. Under similar conditions, the epimeric mixture of keto epoxides **45** and **46** furnished, as expected, diketone **25** as the sole product in 95% yield.

Prior to further discussion, it is deemed appropriate to summarize the results. (-)-Campholenic acid **28**



45



46

obtained from the commercially available (-)-ℓ-camphorsulfonic acid ammonium salt by treatment with molten potassium hydroxide was converted to the corresponding ethyl ketone **29** with ethyllithium. Photo-oxygenation of ketone **29** in dichloromethane in the presence of acetic anhydride, pyridine and 4-dimethylaminopyridine using TPP as a photo-sensitizer gave enone **31** which was subjected to treatment with potassium carbonate in methanol. Epoxidation of the resulting keto alcohol **37** gave the epimeric mixture of epoxy ketones **45** and **46** which underwent rearrangement on exposure to stannic chloride to give hydroxydiketone **25** ($[\alpha]_D^{23}$ = -16.39°, c = 1.55, $CHCl_3$). Thus the B/C ring system of α-patchoulene (**1**) with the correct absolute configuration and the required methyl substituents was established by a six-step synthetic sequence.

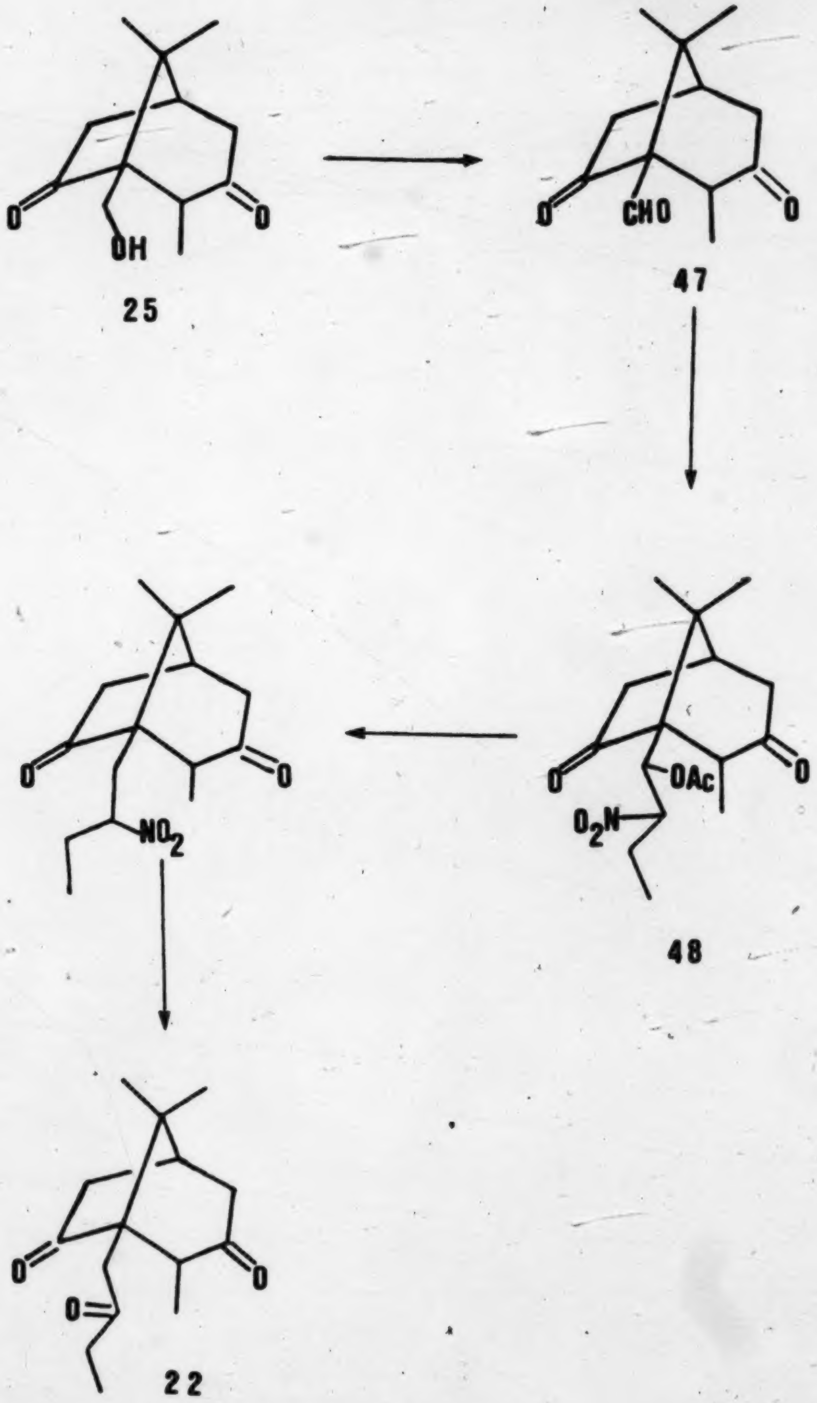
The conversion of hydroxy diketone **25** to the target molecule requires a five-membered ring annelation. Our synthetic plan called for the conversion of the hydroxymethylene substituent to a 2-butanone moiety using nitropropane as an acyl carbanion equivalent as shown in Scheme 12 followed by an intramolecular aldol reaction for ring closure.

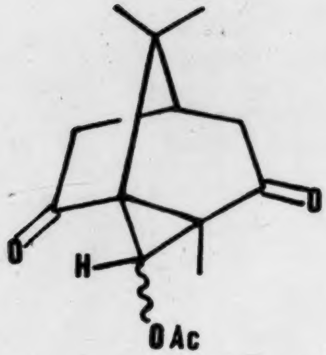
Towards this end, hydroxy diketone **25** was subjected to oxidation with pyridinium chlorochromate[90] in methylene chloride with sodium acetate. The reaction proved to be fruitless. Under normal conditions, the starting material was recovered intact, presumably due to the formation of a stable complex with the assistance of two adjacent carbonyl groups. On the other hand, a complex mixture was produced when the reaction was performed at elevated temperature over a prolonged period of time. Alternatively, hydroxy diketone **25** was oxidized using Swern's modification of the Moffatt oxidation.[75] Thus, compound **25** was treated with a preformed solution of dimethylsulfoxide and oxalyl chloride in methylene chloride at -78°C for 20 min, followed by addition of triethylamine and allowing the reaction mixture to warm up to room temperature. Diketo aldehyde **47** was produced in near-quantitative yield as a mixture of a pair of inseparable epimers (3:1) which showed, in the ^{1}Hmr spectrum, a singlet at δ 9.79 and a doublet (J = 4 Hz) at δ 9.49 in a ratio of 3:1 for a total of one aldehydic proton. Two sets of methyl signals, each consisting of two singlets and a doublet, were also observed with the major signals at δ 1.35, 1.22, and 0.96 (doublet) and the minor ones at δ 1.30, 1.20 (doublet) and 1.11. In agreement with the structural assignment, the mass spectrum showed a molecular ion peak at 208.1094 whereas the ir spectrum exhibited the diagnostic absorption bands at 2830 and 2720 cm^{-1} for the aldehyde group in addition to carbonyl absorptions at 1740 and 1712 cm^{-1}.

Diketo aldehyde **47** was treated with nitropropane and potassium carbonate in methanol[77] in an attempt to extend the aldehydic chain. Acetylation of the crude material gave a major product (72% yield), which was readily identified as the tricyclic diketo acetate **49**, without the formation of the desired nitro acetate **48**. The same result was also obtained when diketo aldehyde **47** was treated with nitropropane and potassium fluoride[91] in isopropyl alcohol followed by acetylation. Diketo acetate **49**, which resulted apparently from an intramolecular aldol condensation of diketo aldehyde **47** and subsequent acetylation of alcohol **50**, was isolated as a single stereoisomer as indicated by the ^{1}Hmr spectrum showing a single set of methyl singlets at δ 2.14, 1.36 (six protons), and 1.19. The stereochemistry of the asymmetric carbon bearing the acetoxy group remains, however, to be determined.

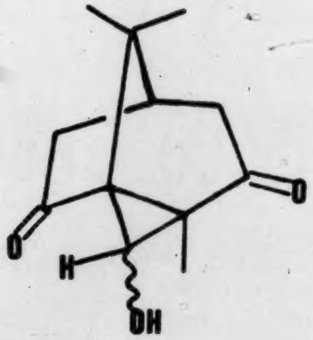
On the basis of the above observations, it became necessary to modify the ketone carbonyl attached to the six-membered ring of diketone alcohol **25**, preferably to the carbon-carbon double bond present in the target molecule, prior to the introduction of the 2-butanone moiety. Initially, diketone alcohol **25** was directly

SCHEME 12


O
OH
O
25
O
CHO
O
47
O
NO$_2$
O
O
OAc
O$_2$N
O
48
O
O
O
22



49

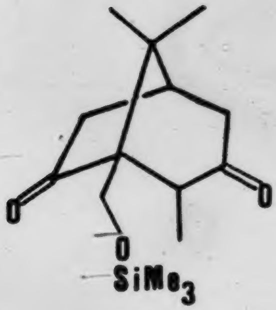


50

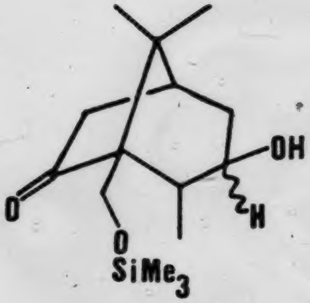
subjected to reduction using sodium borohydride, lithium aluminum hydride or sodium bis(2-methoxyethoxy)aluminum hydride[92] as a reducing agent. In all cases examined, the reaction was found to be non-selective giving rise to a complex mixture of products. To circumvent this problem, the hydroxyl group, which undoubtedly contributed at least in part to the difficulties encountered, was protected in the form of a trimethylsilyl ether. This was effected by brief treatment of compound **25** with triethylamine, 4-dimethylaminopyridine, and trimethylsilyl chloride[93] in methylene chloride at room temperature. Diketo silyl ether **51** thus obtained in 80% yield showed, in the ir spectrum, two intense carbonyl bands at 1740 and 1708 cm^{-1} and the absence of the hydroxy absorption. In the mass spectrum, a molecular ion peak was displayed at 282.1651 corresponding to the required formula of $C_{15}H_{26}O_3Si$. The ^{1}Hmr spectrum showed two three-proton singlets at δ 1.32 and 1.04 due to the gem-dimethyl group, a methyl doublet at δ 0.95 with a coupling constant of 7 Hz, and a high-field singlet (δ 0.04) integrating to nine protons for the trimethylsilyl group.

Selective reduction of diketo silyl ether **51** with one equivalent of lithium tri-tert-butoxyaluminohydride[94] in ether at room temperature gave a 95% yield of two isomeric keto alcohols in a 5:1 ratio; each showed a molecular ion peak at 284.1806 in the mass spectrum. In the ir spectrum, the major isomer, m.p. 113-113.5°C, displayed absorption bands at 3510 and 1734 cm^{-1} for a hydroxyl group and a ketone carbonyl respectively. The ir spectrum of the minor isomer, m.p. 132-133.5°C, was found to be similar with a hydroxy absorption at 3275 cm^{-1} and a carbonyl band at 1727 cm^{-1}. The fact that each of these compounds showed a carbonyl absorption which could be attributed to a cyclopentanone moiety indicated that the desired selective reduction of the six-membered ring ketone of compound **51** had occurred giving rise to a pair of epimeric keto alcohols **52**. As further confirmation of the structural assignments, the ^{1}Hmr spectrum of each epimer showed a nine-proton singlet at δ 0.00 clearly indicating that the trimethylsilyl ether protecting group was intact during the reaction.

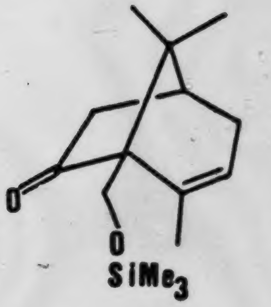
The formation of the epimeric keto alcohols **52** represents the current advance in our studies towards the total synthesis of α-patchoulene (**1**). Further investigation via olefin **53** is currently being carried out in our laboratory.



51



52



53

EXPERIMENTAL

General

For general remarks see the experimental section of Study I of this thesis. Optical rotations were measured using a Perkin-Elmer 141 polarimeter.

Materials

Tetrahydrofuran was freshly distilled from lithium aluminum hydride. Methanol was purified by refluxing and distilling over magnesium turnings. Dichloromethane was washed with 10% sodium carbonate aqueous solution, dried over magnesium sulfate and distilled over calcium chloride. Other solvents were purified by the procedures described in the experimental section Study I. ℓ-10-Camphorsulfonic acid ammonium salt was obtained from Aldrich Chemical Company.

(-)-Campholenic acid (**28**)

Potassium hydroxide (~85% pure; 265 g, ~4 mol) was fused in a ten-inch porcelain casserole with a Bunsen burner. The flame was removed and (-)-ℓ-10-camphorsulfonic acid ammonium salt (**27**) (25 g, 0.1 mol) was added slowly with vigorous stirring over a period of 10 min. The brown solid was heated again with a Bunsen burner until it turned into a yellowish syrup. After the molten mass was cooled to room temperature, water (500 mL) was added slowly to dissolve the hard cake. The resulting solution was extracted with ether (2 x 200 mL). The aqueous layer was cooled to 0°C and acidified with ice-cold 6 N aqueous hydrochloric acid. The acidic solution was extracted with dichloromethane (3 x 100 mL). The organic layer was separated and washed with water (100 mL). The extracts were combined, dried, filtered and concentrated. The crude material was distilled at 102-103°C/2 torr to give the pure acid **28** (16 g; 95% yield): $[\alpha]_D^{23} = -7.0°$ (c = 0.8, $CHCl_3$); ir 3500 (COOH) and 1718 cm^{-1} (C=O); ^{1}Hmr δ 10.90 (br.s, 1H, -COOH), 5.20 (br.s, 1H, =CH-), 1.60 (br.s, 3H, $=\overset{|}{C}CH_3$), 0.99 and 0.77 (both s, 3H each, 2 x $-CH_3$); ms M^+ 168.1150 (calcd. for $C_{10}H_{16}O_2$: 168.1150). Anal. Calcd. for $C_{10}H_{16}O_2$: C 71.38, H 9.59; Found: C 71.42, H 9.63.

4-(2-Oxobutyl)-1,5,5-trimethylcyclopentene (**29**)

(-)-Campholenic acid (4.2 g, 25 mmol) was dissolved in 8 mL of benzene under a nitrogen atmosphere at 0°C. A 0.5 M solution of ethyllithium in pentane (100 mL, 50 mmol) was added slowly over a period of 10 min. The reaction mixture was stirred for 3 h and poured into ice-cold 1 N aqueous hydrochloric acid solution (100 mL) with vigorous stirring. The organic layer was separated and the aqueous layer extracted again with dichloromethane (2 x 20 mL). The organic extracts were washed with brine, combined, dried, filtered and concentrated. The pure ketone **29** was obtained (4.14 g, 92%) after the crude material was purified by column chromatography on silica gel with benzene-hexane (1:19) elution. The following spectral data were recorded for **29**: ir 1702 (C=O) and 1368 cm^{-1} (CH_3); ms M^+ 180.1511 (calcd. for $C_{12}H_{20}O$: 180.1514); ^{1}Hmr δ 5.21 (br.s, 1H, =CH-), 1.61 (br.s, 3H, $=\overset{|}{C}CH_3$), 1.06 (t, 3H, J = 7 Hz, $-CH_2C\underline{H_3}$), 0.99 and 0.78 (both s, 3H each, 2 x $-CH_3$); $[\alpha]_D^{23} = -19.04°$ (c = 1.68, $CHCl_3$). Anal. Calcd. for $C_{12}H_{20}O$: C 79.94, H 11.18; Found: C 80.27, H 11.23.

3,3-Dimethyl-2-methylidene-4-(2-oxobutyl)cyclopentanol (**30**)

A solution of the ketone **29** (3.3 g, 18.3 mmol) and methylene blue (100 mg) in methanol (250 mL) was irradiated with two 200 W tungsten light bulbs for 5 days. During this period a moderate stream of oxygen was bubbled through the solution. Dimethyl sulfide (8 mL, 0.11 mol) was added. After stirring at room temperature for 10 h, the resulting solution was poured into ice-cold 1 N aqueous hydrochloric acid solution (500 mL) and extracted with dichloromethane (3 x 150 mL). The extracts were washed with water, combined, dried, filtered and concentrated. The residue was chromatographed on silica gel. Elution with a solution of 5% ether in hexane gave the starting material **29** (363 mg, 11% recovery). Further elution with a solution of 40% ether in hexane afforded an epimeric mixture of allylic alcohols **30** (2.6 g, 73% yield): ir 3420 (OH) and 1702 cm^{-1} (C=O); ms M^+ 196.1463 (calcd. for $C_{12}H_{20}O_2$: 196.1456); ^{1}Hmr δ 5.17, 4.98 (both br.s, 1H each, $=CH_2$), 4.44 (br.d, 1H, J = 7 Hz, $-\overset{|}{C}HO-$), 1.14, 0.84 (both s, 2.7 H each, 2 x $-CH_3$), 1.08, 0.87 (both s, 0.3 H each, 2 x $-CH_3$), 1.06 (t, 2.7 H, J = 8 Hz, $-CH_2C\underline{H_3}$), and 0.94 (t, 0.3 H, J = 8 Hz, $-CH_2C\underline{H_3}$). When the chromatography was carried out very slowly, the major epimer could be isolated in pure form and showed $[\alpha]_D^{23}$ = -42.94° (c = 0.34, $CHCl_3$). The ir and mass spectra were found to be similar to those of the mixture. The ^{1}Hmr signals were identical to those of the major component of the epimeric mixture: δ 5.17, 4.98 (both d, 1H each, J = 1.7 Hz each, $=CH_2$), 4.51 (dd, 1H, J = 7, J' = 3 Hz, $-\overset{|}{C}HO-$), 1.14, 0.84 (both s, 3H each, 2 x $-CH_3$), and 1.06 (t, 3H, J = 8 Hz, $-CH_2\underline{CH_3}$).

3,3-Dimethyl-2-methylidene-4-(2-oxobutyl)cyclopentanone (31)

(a) From alcohols 30

At -78°C, oxalyl chloride (0.55 mL, 6.3 mmol) was dissolved in dichloromethane (10 mL) under a nitrogen atmosphere. A solution of DMSO (0.98 mL, 13.8 mmol) in dichloromethane (5 mL) was added dropwise over a period of 5 min with stirring. After 20 min, a solution of allylic alcohols **30** (1.12 g, 5.7 mmol) in dichloromethane (5 mL) was added slowly over a period of 15 min. The resulting milky solution was stirred for 10 min and then a solution of triethylamine (3.8 mL, 27.3 mmol) in dichloromethane was introduced in a dropwise manner over a 20 min period. The solution was allowed to warm up slowly to room temperature. The yellowish solution thus obtained was stirred for 2 h, poured into ice-cold 1 N aqueous hydrochloric acid solution (30 mL) and extracted with dichloromethane (3 x 10 mL). The extracts were washed with brine, combined, dried, filtered and concentrated. The crude material was purified by medium pressure flash chromatography on silica gel. Elution with a solution of 10% ether in hexane gave α,β-unsaturated ketone **31** (1.03 g; 93% yield): ir 1728 (enone C=O), 1710 (C=O) and 1634 cm^{-1} (C=C); ms M^+ 194.1306 (calcd. for $C_{12}H_{18}O_2$: 194.1307); ^{1}Hmr δ 5.95, 5.18 (both s, 1H each, $=CH_2$), 1.22, 1.01 (both s, 3H each, 2 x $-CH_3$), and 1.07 (t, 3H, J = 8 Hz, $-CH_2\underline{CH_3}$).

(b) From ketone **29**

A solution of the ketone **29** (967 mg, 5.4 mmol), acetic anhydride (0.55 mL, 5.9 mmol), pyridine (0.47 mL, 5.9 mmol), TPP (10 mg) and DMAP (12 mg) in dichloromethane (200 mL) was irradiated with two 200 W tungsten light bulbs for 8 h. During this period a moderate stream of oxygen was bubbled through the solution. After stirring at room temperature for an additional period of 8 h, the reaction mixture was washed with water (2 x 50 mL). The organic solution was dried, filtered and concentrated. The residue was dissolved in methanol (10 mL), filtered through celite 545, and concentrated. Chromatography of the residue on silica gel, eluting with a solution of 5% ether in hexane gave the starting material **29** (174 mg, 18% recovery). Further elution with a solution of 20% ether in hexane afforded α,β-unsaturated ketone **31** (636 mg, 60% yield).

3,3-Dimethyl-2-(2-nitrobutyl)-4-(2-oxobutyl)cyclopentanone (**32**)

Anhydrous potassium carbonate (200 mg, 1.45 mmol) was added to a solution of nitropropane (2.3 mL, 25 mmol) in methanol (20 mL). A solution of α,β-unsaturated ketone **31** (2.03 g, 10.5 mmol) in methanol (3 mL) was then added. The reaction mixture was stirred at room temperature under an argon atmosphere for 16 h, then poured into water (50 mL), and extracted with dichloromethane (3 x 15 mL). The extracts were washed with water, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 40% ether in hexane afforded nitro ketones **32** (2.9 g; 98% yield): ir 1732, 1708 (C=O) and 1542 cm^{-1} (NO_2); ms m/e 282.1698 (M^+-1, calcd. for $C_{15}H_{24}NO_4$: 282.1705). Recrystallization from ether-hexane gave white solids, m.p. 82-83°C, which showed the same ir and ms spectral data. In the ^{1}Hmr spectrum, the following signals were observed: δ 4.90 (br.m, 1H, $-\overset{|}{C}HNO_2$), 1.06, 0.64 (both.s, 3H each, 2 x $-CH_3$), 0.98 and 0.89 (both s, 3H each, J = 8 Hz each, $-CH_2\underline{CH_3}$). Anal. Calcd. for $C_{15}H_{25}NO_4$: C 63.58, H 8.89, N 4.94; Found: C 63.29, H 8,90, N 4.82.

3,3-Dimethyl-2,4-bis(2-oxobutyl)cyclopentanone (**26**)

Nitro ketone **32** (252 mg, 0.9 mmol) was dissolved in methanol (5 mL) and a 1.4 M solution of sodium methoxide in methanol (0.8 mL, 1.12 mmol) was added. At -78°C, ozone (conditions: E = 80 V, air inlet = 8 psi, ozone outlet = 0.06 psi) was allowed to pass through this solution until a blue color was retained. After 15 min, the reaction mixture was purged with argon to remove excess ozone. Dimethyl sulfide (2 mL) was then added. The mixture was stirred at room temperature for 7 h, acidified with ice-cold 1 N aqueous hydrochloric acid (20 mL), and extracted with dichloromethane (3 x 10 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 25% ether in hexane gave rise to the triketone **26** (197 mg; 87% yield): m.p. 68-69°C (ether-pet. ether); ir 1736 and 1708 cm^{-1} (C=O); ms M$^+$ 252.1728 (calcd. for $C_{15}H_{24}O_3$:

252.1725); ^{1}Hmr δ 1.16, 0.98 (both t, J = 7 Hz each, 2 x $-CH_2\underline{CH_3}$), 1.05 and 0.65 (both s, 3 H each, 2 x $-CH_3$).

1-Hydroxy-2,6,6-trimethyl-7-methylidenebicyclo[3.2.1]-octan-3-one (**37**)

Anhydrous potassium carbonate (100 mg, 0.73 mmol) was added to a solution of α,β-unsaturated ketone **31** (1.02 g, 5.3 mmol) in methanol (5 mL). After stirring at room temperature for 4 h, the mixture was poured into water (30 mL) and extracted with dichloromethane (2 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The residue was subjected to column chromatography on silica gel. Elution with a solution of 20% ether in hexane afforded the starting material **31** (255 mg; 25% recovery). Further elution with a solution of 30% ether in hexane gave a mixture of epimeric diketones **39** (297 mg; 25% yield): ir 1740 and 1717 cm^{-1} (C=O); ms M$^+$ 226.1561 (calcd. for $C_{13}H_{22}O_3$: 226.1569); ^{1}Hmr δ 4.53 (m, 2H, $-OCH_2-$), 4.29 (s, 3H, $-OCH_3$), 1.17, 0.70 (both s, 3H each, 2 x $-CH_3$), and 1.02 (t, 3H, J = 7 Hz, $-CH_2\underline{CH_3}$). Further elution with a solution of 40% ether in hexane gave rise to keto alcohol **37** (510 mg; 50% yield): m.p. 95-96°C (ether-pet. ether); ir 3445 (OH), 1702 (C=O) and 1655 cm^{-1} (C=C); ms M$^+$ 194.1306 (calcd. for $C_{12}H_{18}O_2$:

194.1307); ^{1}Hmr δ 5.00, 4.96 (both s, 1H each, $=CH_2$), 1.12, 0.94 (both s, 3H each, 2 x $-CH_3$), and 1.02 (d, 3H, J = 7 Hz, $-\overset{|}{C}HC\underline{H}_3$).

1,2,8,8-Tetramethyl-3-propanoyloxybicyclo[3.2.1]oct-2-en-7-one (**40**)

At 0°C, keto alcohol **37** (457 mg, 2.36 mmol) was dissolved in chloroform (6 mL) under an argon atmosphere. Propionyl chloride (0.62 mL, 7.1 mmol) and stannic chloride (0.83 mL, 7.1 mmol) were added to the solution. After stirring for 4 h at room tempreature, water (20 mL) and then ice-cold 1 N aqueous hydrochloric acid (30 mL) were added. The mixture was extracted with dichloromethane (3 x 10 mL). The extracts were washed with saturated aqueous sodium carbonate solution, water, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with a solution of 30% ether in hexane afforded enol propionate **40** (531 mg; 90% yield): ir 1750 (ester C=O), 1734 (C=O) and 1686 cm^{-1} (C=C); ms M^+ 250.1569 (calcd. for $C_{15}H_{22}O_3$: 250.1569); ^{1}Hmr δ 2.70 (ddt, 1H, J = 17, J' = 4, J" = 2 Hz, $=\overset{|}{C}-\overset{|}{C}H-$), 2.53 (dd, 1H, J = 19, J' = 7 Hz, $-CO\overset{|}{C}H-$), 2.43 (q, 2H, J = 8 Hz, $-COC\underline{H_2}CH_3$), 2.22 (d, 1H, J = 19 Hz, $-CO\overset{|}{C}H-$), 1.98 (ddd, 1H, J = 7, J' = 4, J" = 2 Hz,

$-CH_2-\overset{|}{C}\underline{H}-CH_2-$), 1.91 (dt, 1H, J = 17, J' = 2 Hz, $=\overset{|}{C}-\overset{|}{C}H-$), 1.43 (t, 3H, J = 2Hz, $=\overset{|}{C}CH_3$), 1.17 (t, 3H, J = 8 Hz, $-CH_2C\underline{H_3}$), 1.06, 1.03 and 0.85 (all s, 3H each, 3 x $-CH_3$); ^{13}Cmr δ 211.0, 172.4, 143.4, 121.5, 57.0, 41.9, 40.9, 38.4, 33.9, 27.4, 25.0, 18.8, 11.4, 9.5, and 9.1.

1,2,8,8-Tetramethylbicyclo[3.2.1]octane-3,7-dione (**41**)

Enol propionate **40** (190 mg, 0.76 mmol) was dissolved in methanol (4 mL). A solution of sodium methoxide in methanol (1.2 M, 1 mL, 1.2 mmol) was added. The reaction mixture was brought to reflux. After 3 h, the mixture was acidified with ice-cold 1 N aqueous hydrochloric acid (20 mL) and extracted with dichloromethane (2 x 10 mL). The extracts were washed with water, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with 10% ether in hexane gave rise to diketone **41** (147 mg; 100% yield): ir 1738 and 1702 cm^{-1} (C=O); ms M$^+$ 194.1302 (calcd. for $C_{12}H_{18}O_2$: 194.1307); ^{1}Hmr δ 1.96 (d, 1H, J = 19 Hz, $-\underset{|}{\overset{|}{C}}-COC\underline{H}H-$), 1.23, 0.99, 0.97 (all s, 3H each, 3 x $-CH_3$), and 0.98 (d, 3H, J = 7 Hz, $-\overset{|}{C}H-C\underline{H_3}$).

2,6,6-Trimethyl-7-methylidene-1-propanoyloxybicyclo[3.2.1]octan-3-one (**42**)

(A) From Stannic Chloride and Propionyl Chloride

Keto alcohol **37** (186 mg, 0.96 mmol) was dissolved in dichloromethane (3 mL). Propionyl chloride (0.1 mL, 1.15 mmol) and stannic chloride (0.1 mL, 0.86 mmol) were added to the solution at 0°C under an argon atmosphere. After stirring for 45 min at 0°C, water and then ice-cold 1N aqueous hydrochloric acid (30 mL) were added. The mixture was extracted with dichloromethane (3 x 10 mL). The extracts were washed with saturated aqueous sodium carbonate solution and water, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with 5% ether in hexane gave propionate **42** (228 mg; 95% yield): ir 1731, 1708 (C=O) and 1652 cm^{-1} (C=C); ms M^+ 250.1567 (calcd. for $C_{15}H_{22}O_3$: 250.1569); ^{1}Hmr δ 5.01 (s, 2H, $=CH_2$), 1.23, 0.99 (both s, 3H each, 2 x $-CH_3$), 1.60 (t, 3H, J = 7.5 Hz, $-CH_2C\underline{H}_3$), and 0.96 (d, 3H, J = 7 Hz, $-\overset{|}{C}-C\underline{H}_3$).

(B) From Pyridine and Propionyl Chloride

Keto alcohol **37** (194 mg, 1 mmol) was dissolved in dichloromethane (3 mL). Propionyl chloride (0.1 mL, 1.15

mmol) and pyridine (0.1 mL, 1.26 mmol) were added at 0°C under a nitrogen atmosphere. After stirring for 8 h at room temperature, ice-cold 1 N aqueous hydrochloric acid (20 mL) was added. The mixture was extracted with dichloromethane (3 x 10 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with 5% ether in hexane afforded propionate **42** (250 mg; 100% yield).

1-Acetoxy-2,6,6-trimethyl-7-methylidenebicyclo-[3.2.1]octan-3-one (**43**)

Keto alcohol **37** (122 mg, 0.63 mmol) was dissolved in dichloromethane (3 mL). Acetyl chloride (0.06 mL, 0.84 mmol) and pyridine (0.1 mL, 1.26 mmol) were added to the solution at 0°C under a nitrogen atmosphere. After stirring for 8 h at room temperature, ice-cold 1 N aqueous hydrochloric acid (30 mL) was added. The mixture was extracted with dichloromethane (3 x 10 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel. Elution with 5% ether in hexane gave acetate **43** (148 mg; 100% yield): ir 1730, 1708 (C=O) and 1652 cm^{-1} (C=C); ms M^+ 236.1413 (calcd. for

$C_{14}H_{20}O_3$: 236.1412); ^{1}Hmr 5.18, 5.06 (both d, 1H each, J = 2 Hz each, $=CH_2$), 2.06 (s, 3H, $-COCH_3$), 1.14, 0.86 (both s, 3H each, 2 x $-CH_3$), and 1.04 (d, 3H, J = 6 Hz, $-\overset{|}{C}HC\underline{H}_3$).

Spiro(1-hydroxy-2,6,6-trimethylbicyclo[3.2.1]octan-3-one)-7,2'-oxirane (**24**)

m-Chloroperbenzoic acid (ca. 80% pure, 236 mg, ~ 1.1 mmol) was added to a solution of keto alcohol **37** (194 mg, 1 mmol) in dichloromethane (5 mL). After stirring for 3 h under an argon atmosphere at room temperature, a 10% aqueous sodium sulfite solution (20 mL) was added. The organic layer was separated and washed with 10% aqueous sodium bicarbonate solution (20 mL). The aqueous layer was extracted with dichloromethane (2 x 10 mL). The organic solution was washed with brine, dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 35% ether in hexane, to give a mixture of epoxy alcohols **24** (179 mg; 85% yield): ir 3494 (OH) and 1704 cm^{-1} (C=O); ms M^+ 210.1264 (calcd. for $C_{12}H_{18}O_3$: 210.1256); ^{1}Hmr δ 2.93, 2.81 (both d, 1H each, J = 4 Hz each, $-CH_2-O$), 1.60 (br.s, 1H, -OH), 1.28 (d, 9/5H, J = 7 Hz, $-\overset{|}{C}HC\underline{H}_3$), 1.11 (d, 6/5H, J = 7 Hz, $-\overset{|}{C}HC\underline{H}_3$), 1.02, 0.9 (both s, 9/5H each, 2 x $-CH_3$), 0.96 and 0.89

(both s, 6/5H each, 2 x $-CH_3$). Anal. Calcd. for $C_{12}H_{18}O_3$: C 68.54, H 8.63; Found: C 68.29, H 8.65.

1-Hydroxymethyl-2,8,8-trimethylbicyclo[3.2.1]octane-3,7-dione (25)

Stannic chloride (0.1 mL) was added to a solution of epoxy alcohols **24** (105 mg, 0.5 mmol) in chloroform (3 mL). After stirring for 8 h under a nitrogen atmosphere at room temperature, water (10 mL) was added. The resulting solution was then poured into ice-cold 1 N aqueous hydrochloric acid (50 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were washed with water, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel. Elution with a solution of 40% ether in hexane afforded diketo alcohol **25** (95 mg; 95% yield): m.p. 96-97°C (ether-pet. ether); $[\alpha]_D^{23} = -16.39°$ (c = 1.55, $CHCl_3$); ir 3945 (OH), 1732 and 1703 cm^{-1} (C=O); ms M^+ 210.1257 (calcd. for $C_{12}H_{18}O_3$: 210.1256); ^{1}Hmr δ 3.93, 3.84 (both d, 1H each, J = 11 Hz each, $-C\underline{H_2}OH$), 3.01 (q, 1H, J = 7 Hz, $-\overset{|}{C}\underline{H}CH_3$), 2.86 (ddd, 1H, J = 17, J' = 3.5, J" = 3 Hz, $-\overset{|}{C}HCOC\underline{H}H-$), 2.60 (ddd, 1H, J = 19, J' = 8, J" = 3 Hz, $-\overset{|}{\underset{|}{C}}-COC\underline{HH}-$), 2.38 (dd, 1H, J = 17, J' = 3 Hz, $-\overset{|}{C}HCOCH\underline{H}-$), 2.19 (ddd, 1H, J = 8, J' = 3.5, J" = 3 Hz, $-CH_2\overset{|}{C}\underline{H}CH_2-$), 1.96 (d, 1H, J = 19 Hz, $-\overset{|}{\underset{|}{C}}-CO\overset{|}{C}H-$, 1.79 (br.s, 1H, -OH), 1.43, 1.16 (both s, 3H each, 2 x $-CH_3$), and 1.08 (d, 3H, J = 7 Hz, $-\overset{|}{C}HC\underline{H}_3$). *Anal*. Calcd. for $C_{12}H_{18}O_3$: C 68.54, H 8.63; Found: C 68.75, H 8.82.

Spiro(1-hydroxy-2,6,6-trimethylbicyclo[3.2.1]octan-3-one)-7,2'-oxirane (**46**) and 1-Hydroxymethyl-2,8,8-trimethylbicyclo[3.2.1]octane-3,7-dione (**25**)

m-Chloroperbenzoic acid (*ca*. 80% pure, 236 mg, ~ 1.1 mmol) was added to a solution of keto alcohol **36** (194 mg, 1 mmol) in dichloromethane (5 mL). After stirring for 16 h under an argon atmosphere at room temperature, barium hydroxide (1 g, 13.5 mmol) was added. The mixture was allowed to stir for 10 min and filtered. The residue was washed thoroughly with dichloromethane (20 mL). The filtrate was concentrated and the crude product purified by column chromatography on silica gel. Elution with 35% ether in hexane afforded an epoxy alcohol **46** (71 mg; 34% yield): m.p. 117-118°C (ether-pet. ether); ir 3495 (OH) and 1704 cm^{-1} (C=O); ms M^+ 210.1258 (calcd. for $C_{12}H_{18}O_3$: 210.1256); ^{1}Hmr δ 2.93, 2.81 (both d, 1H each, J = 4 Hz, $-CH_2-O$), 1.11 (d, 3H, J = 7 Hz, $-\overset{|}{C}-HC\underline{H}_3$), 0.96 and 0.89 (both s, 3H each, 2 x $-CH_3$). Further elution with 40% ether in hexane gave diketo alcohol **25** (107 mg; 51% yield).

1-Formyl-2,8,8-trimethylbicyclo[3.2.1]octane-3,7-dione (47)

Oxalyl chloride (0.14 mL, 1.6 mmol) was dissolved in dichloromethane (10 mL) at -78°C under a nitrogen atmosphere and a solution of DMSO (0.25 mL, 3.5 mmol) in dichloromethane (5 mL) was added dropwise over a period of 5 min. After stirring for 20 min, a solution of diketo alcohol **25** (300 mg, 1.4 mmol) in dichloromethane (5 mL) was added slowly. The reaction mixture was stirred for another 20 min and a solution of triethylamine (0.95 mL, 6.8 mmol) in dichloromethane (10 mL) was introduced. The mixture was allowed to warm up slowly to room temperature. The resulting mixture was poured into ice-cold 1 N aqueous hydrochloric acid (30 mL) and extracted with dichloromethane (2 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The residue was purified by column chromatography on silca gel. Elution with a solution of 20% ether in hexane afforded a mixture of aldehydes **47** (285 mg; 98% yield): ir 2830, 2720 (-CHO), 1740 and 1712 cm^{-1} (C=O); ms M$^+$ 208.1094 (calcd. for $C_{12}H_{16}O_3$: 208.1099); ^{1}Hmr δ 9.79 (s,

3/4H, -CHO), 9.49 (d, 1/4H, J = 4 H, -CHO), 3.10 (br.q, 1H, J = 7 Hz, $-\overset{|}{C}HCH_3$), 2.12 (d, 1H, J = 19 Hz, $-\overset{|}{\underset{|}{C}}-COC\underline{H}H-$), 1.35, 1.22 (both s, 9/4H each, 2 x $-CH_3$), 1.30, 1.11 (both s, 3/4H each, 2 x $-CH_3$), 1.20 (d, 3/4H, J = 7 Hz, $-\overset{|}{C}HC\underline{H_3}$) and 0.96 (d, 9/4H, J = 7 Hz, $-\overset{|}{C}HC\underline{H_3}$).

2-Acetoxy-3,9,9-trimethyltricyclo[4.2.1.0^{1,3}]nonane-4,8-dione (**49**)

Potassium fluoride (20 mg, 0.34 mmol) was added to a solution of aldehydes **47** (260 mg, 1.25 mmol) and 1-nitropropane (0.22 mL, 2.5 mmol) in 2-propanol (5 mL). The reaction mixture was stirred at room temperature under an argon atmosphere for 6 h. The solvent was evaporated under reduced pressure. Ether (10 mL) was introduced followed by the addition of DMAP (12 mg, 0.1 mmol) and acetic anhydride (0.3 mL, 1 mmol). The resulting mixture was stirred for another 20 h, then poured into ice-cold 1 N aqueous hydrochloric acid and extracted with dichloromethane (3 x 10 mL). The extracts were washed wtih brine, dried, filtered and concentrated. The residue was chromatographed on silica gel. Elution with a solution of 30% ether in hexane gave diketo acetate **49** (225 mg; 72% yield): ir 1745 and 1715 cm^{-1} (C=O); ms M$^+$ 250.1206 (calcd. for $C_{14}H_{18}O_4$: 250.1205); ^{1}Hmr δ 6.95 (s, 1H, $-\overset{|}{\mathrm{C}}\mathrm{HO}-$), 2.14 (s, 3H, $-\mathrm{COCH_3}$), 1.36 (s, 6H, 2 x $-\mathrm{CH_3}$), 1.19 (s, 3H, $-\mathrm{CH_3}$).

2,8,8-Trimethyl-1-trimethylsilyloxymethylbicyclo[3.2.1]octane-3,7-dione (**51**)

Diketo alcohol **25** (1.119 g, 5.33 mmol) was dissolved in dichloromethane (30 mL). DMAP (80 mg, 0.65 mmol) and triethylamine (1.48 mL, 10.6 mmol) were added. The resulting mixture was cooled to 0°C under a nitrogen atmosphere and trimethylsilyl chloride (2.7 mL, 21.2 mmol) was added. After stirring at room temperature for 2 h, an ice-cold 1 N aqueous hydrochloric acid (30 mL) was added. The resulting solution was extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with 30% ether in hexane gave diketo silyl ether **51** (1.2 g; 80% yield): ir 1740 (C=O) and 1708 $\mathrm{cm^{-1}}$ (C=O); ms M^+ 282.1651 (calcd. for $\mathrm{C_{15}H_{26}SiO_3}$: 282.1651); ^{1}Hmr δ 3.78, 3.53 (both d, 1H each, J = 11 Hz, $-\mathrm{CH_2O}-$), 1.32, 1.04 (both s, 3H each, 2 x $-\mathrm{CH_3}$), 0.95 (d, 3H, J = 7 Hz, $-\overset{|}{\mathrm{C}}\mathrm{HC}\underline{\mathrm{H_3}}$), and 0.04 (s, 9H, 3 x $\mathrm{CH_3}$).

3-Hydroxy-2,8,8-trimethyl-1-trimethylsilyloxybicyclo[3.2.1]octan-7-one (**52**)

Diketo silyl ether (564 mg, 2 mmol) was dissolved in ether (5 mL). Lithium tri-tert-butoxyaluminohydride (508 mg, 2 mmol) was added at 0°C under an argon atmosphere. After stirring for 2 h at room temperature, the resulting mixture was poured into water. The solution was extracted with dichloromethane (3 x 20 mL). The extracts were washed with brine, dried, fltered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with 40% ether in hexane gave the major epimer of keto alcohols **52** (450 mg; 79% yield): m.p. 113-113.5°C (ether-pet. ether); ir 3510 (OH) and 1734 cm^{-1} (C=O); ms M^+ 284.1809 (calcd. for $C_{15}H_{28}O_3Si$: 284.1807); ^{1}Hmr 3.88 (br.t, 1H, J = 4 Hz, $-\overset{|}{C}\underline{H}OH$), 3.74, 3.41 (both d, 1H each, J = 11 Hz, $-CH_2-O-$), 1.12, 0.89 (both s, 3H each, 2 x $-CH_3$), 0.91 (d, 3H, J = 7 Hz, $-\overset{|}{C}HC\underline{H_3}$) and 0.00 (s, 9H, $-Si(CH_3)_3$). Further elution with 40% ether in hexane afforded the minor epimer of **52** (90 mg; 16% yield): m.p. 132-133.5°C (ether-pet. ether); ir 3275 (OH) and 1727 cm^{-1} (C=O); ms M^+ 284.1806 (calcd. for $C_{15}H_{28}O_3Si$: 284.1807); ^{1}Hmr 3.86, 3.38 (both d, 1H each, J = 11 Hz, $-CH_2-O-$), 3.28 (br.dd, 1H, J = 18, J' = 11 Hz, $-\overset{|}{C}\underline{H}OH$), 1.16, 0.85 (both s, 3H each, 2 x $-CH_3$), 0.86 (d, 3H, J = 7 Hz, $-\overset{|}{C}HC\underline{H_3}$), and 0.00 (s, 9H, $-Si(CH_3)_3$).

REFERENCES

1. Muhler, Ann., **176**, 181 (1875).
2. A.W. Ralston, E.W. Segebrecht, and S.T. Bauer, J. Org. Chem., **4**, 502 (1939) and references cited therein.
3. J. Bougault, E. Cattelain, and P. Chablier, Bull. Soc. Chim. Fr., **5**, 1699 (1938).
4. R. Mozingo, D.E. Wolf, S.A. Harris, and K. Folkers, J. Am. Chem. Soc., **65**, 1013 (1943).
5. M. Raney, U.S. Patent, 1628190 (1927).
6. M.L. Wolfrom and J.V. Karabinos, J. Am. Chem. Soc., **68**, 1455 (1946).
7. O. Jeger, J. Norymberski, S. Szipilfogel, and V. Prelog, Helv. Chim. Acta., **29**, 360 (1946).
8. V. Prelog, J. Norymberski, and O. Jeger, Helv. Chim. Acta., **29**, 684 (1946).
9. A.V. McIntosh, Jr., E.M. Meinzer, and R.H. Levin, J. Am. Chem. Soc., **70**, 2955 (1948).
10. A.V. McIntosh, Jr., A.M. Searcy, E.M. Meinzer, and R.H. Levin, J. Am. Chem. Soc., **71**, 3317 (1949).
11. T. Kumamoto and T. Mukaiyama, Bull. Chem. Soc. Jpn., **41**, 2111 (1968).
12. T. Mukaiyama, Angew. Chem., Int. Ed. Engl., **18**, 707 (1979).

13. T. Mukaiyama, T. Takeda and K. Atsummi, Chem. Letters, 187 (1974).

14. S. Yamada, Y. Yokoyama, and T. Shioiri, J. Org. Chem., **39**, 3302 (1974).

15. T. Shiori, Y. Yokoyama, Y. Kasai, and S. Yamada, Tetrahedron, **32**, 2211 (1976).

16. H.J. Liu, S.P. Lee, and W.H. Chan, Synth. Commun., **9**, 91 (1979).

17. H.J. Liu and S.I. Sabesan, Can. J. Chem., **58**, 2645 (1980).

18. A. Arrieta, T. Garcia, J.M. Lago, and C. Palomo, Synth. Commun., **13**(6), 471 (1983).

19. M. Sekine, A. Kume and T. Hata, Tetrahedron Lett., 3617 (1981).

20. S. Masamune, C.U. Kim, K.E. Wilson, G.O. Spessard, P.E. Georgion, and G.S. Bates, J. Am. Chem. Soc., **97**, 3512 (1975).

21. S. Masamune, H. Yamamoto, S. Kamata, and A. Fukuzawa, J. Am. Chem. Soc., **97**, 3513 (1975).

22. S. Masamune, S. Kamata, and W. Schilling, J. Am. Chem. Soc., **97**, 3715 (1975).

23. S. Kim and S. Yang, Chem. Letters, 133 (1981).

24. H.J. Gais, Angew. Chem., Int. Ed. Engl. **16**, 244 (1977).

25. M. Ueda, K. Seki, and Y. Imai, Synthesis, 991 (1981).

26. K.C. Nicolau, Tetrahedron, **33**, 683 (1977).

27. T.G. Back, Tetrahedron, **33**, 3041 (1977).

28. E.J. Corey and N.C. Nicolau, J. Am. Chem. Soc., **46**, 5614 (1974).

29. E.J. Corey, D.J. Brunelle, and P.J. Stork, Tetrahedron Lett., 3405 (1976).

30. H. Gerlach and A. Thalmann, Helv. Chim. Acta., **57**, 293 (1974).

31. E.J. Corey and S. Bhattacharyya, Tetrahedron Lett., 3919 (1977).

32. S. Masamune, Y. Hayase, W. Schilling, W.K. Chan, and G.S. Bates, J. Am. Chem. Soc., **99**, 6756 (1977).

33. I. Ernest, J. Gostelic, C.W. Greengrass, W. Holick, D.E. Jackman, H.R. Pfaendler, and R.B. Woodward, J. Am. Chem. Soc., **100**, 8214 (1978).

34. R.J. Anderson, C.A. Henrick, and L.D. Rosenblum, J. Am. Chem. Soc., **96**, 3654 (1974).

35. H.J. Liu and H.K. Lai, Can. J. Chem., **57**, 2522 (1979).

36. H.J. Liu and H.K. Lai, Synth. Commun., **11**, 65 (1981).

37. H.J. Liu, S.K. Attah-Poku, and H.K. Lai, Synth. Commun., **9**, 883 (1979).

38. H.J. Liu, H.K. Lai and S.K. Attah-Poku, Tetrahedron Lett., 4121 (1979).

39. H.J. Liu and I.V. Oppong, Can. J. Chem., **60**, 94 (1982).

40. Y. Nagao, K. Kawabata, and E. Fujita, Chem. Commun., 330 (1978).

41. H.J. Liu and H. Wynn, Tetrahedron Lett., **23**, 3151 (1982).

42. H.J. Liu, L.K. Ho, and H.K. Lai, Can. J. Chem., **59**, 1685 (1981).

43. H.J. Liu and L.K. Ho, Can. J. Chem., **61**, 632 (1983).

44. H.J. Liu and H.K. Lai, Tetrahedron Lett., 1193 (1979).

45. R.E. Gawley, Synthesis, 777 (1976).

46. M.E. Jung, Tetrahedron, 3 (1976).

47. J.A. Marshall and D.J. Schaeffer, J. Org. Chem., **30**, 3642 (1965).

48. J.A. Peters, Synthesis, 321 (1979).

49. G. Posner in "Organic reactions," Vol. 19, J. Wiley and Sons, Inc., New York, N.Y. 1972. Chapt. 1.

50. W.F. Gannon and H.O. House, Org. Synth. **40**, 14 (1960).

51. A.P. Krapcho, J. Diamanti, C. Cayen, and R. Bingham, Org. Synth., **47**, 20 (1967).

52. T.K. Devon and A.I. Scott, "Handbook of naturally occurring compounds," Vol. II, Terpenes, Academic press, New York, N.Y. 1972.

53. R.J. Anderson, C.A. Henrick, J.B. Siddall, and R. Zurflüh, J. Am. Chem. Soc., **94**, 5379 (1972).

54. E. Breitimier and W. Voelter, "^{13}C NMR Spectroscopy," 2nd ed., Verlag Chemie, Weinheim, N.Y. (1978).

55. R.M. Magid, Tetrahedron, **36**, 1901 (1980).

56. R.G. Jones and H. Gilman in "Organic Reactions," Vol. VI, J. Wiley and Sons, Inc., New York, N.Y. 1951. p. 339.

57. R.G. Jones and H. Gilman, Chem. Rev., **54**, 841 (1954).

58. G. Ruecker, J. Tautges, M.L. Maheswari, and D.B. Saxena, Phytochemistry, **15**, 224 (1976).

59. G. Büchi, R.E. Erickson, and N. Wakabayashi, J. Am. Chem. Soc., **83**, 927 (1961).

60. N. Tsubaki, K. Nishimura, and Y. Hirose, Bull. Chem. Soc. Jpn., **40**, 597 (1967).

61. W. Treibs, Ann., **564**, 141 (1949).

62. M. Dobler, J.D. Dunitz, and B. Gubler, H.P. Weber, G. Büchi, and J. Padilla O., Proc. Chem. Soc., 383 (1963).

63. G. Büchi, W.D. MacLeod, Jr., and J. Padilla O., J. Am. Chem. Soc., **86**, 4438 (1964).

64. O. Metl, B. Trivedi, V. Herout, and F. Sorm, Chem. Ind. (London), 1284 (1963).

65. H. Hikino, K. Ito, K. Aota, and T. Takemoto, Chem. Pharm. Bull., **16**, 43 (1968).

66. H. Hikino, K. Aota, and T. Takemoto, Chem. Pharm. Bull., **16**, 52 (1968).

67. H. Hikino, K. Aota, and T. Takemoto, Tetrahedron, **23**, 2169 (1967).

68. P. Deslongchamps, J. Lafontaine, L. Ruest, and P. Soucy, Can. J. Chem., **55**, 4117 (1977).

69. W.F. Erman and L.C. Stone, J. Am. Chem. Soc., **93**, 2821 (1971).

70. W.H. Chan, Ph.D. thesis, University of Alberta, (1979).

71. M.J. Jorgenson, Org. Reactions, **18**, 1 (1970).

72. M.S. Kharasch, R.A. Mosher, and I.S. Bengelsdorf, J. Org. Chem., **25**, 1000 (1960).

73. H.H. Wasserman and J.L. Ives, Tetrahedron, **37**, 1825 (1981).

74. L. Syper, Tetrahedron Letters, 4493 (1966).

75. A.J. Maucuso, D.S. Brownsfain, and D. Swern, J. Org. Chem., **44**, 4148 (1978).

76. E.D. Mihelich and D.J. Eickhoff, J. Org. Chem., **48**, 4135 (1983).

77. J.E. McMurry, J. Melton, and H. Padgett, J. Org. Chem., **39**, 259 (1974).

78. E.A. Braude, L.M. Jackman, R.P. Linstead, and G. Lowe, J. Chem. Soc., 3123, 3133 (1960).

79. P. Morand, S. Stavrit, and D. Godin, Tetrahedron Letters, 49 (1966).

80. J.C. Banerji, D.H.R. Barton, and R.C. Cookson, J. Chem. Soc., 5041 (1957).

81. C.W. Shoppee, A.B. Devine, and R.E. Lack, J. Chem. Soc., 6458 (1965).

82. P.A. Grieco and M. Nishizawa, J.C.S. Chem. Comm., 582 (1976).

83. R.L. Wasson and H.O. House, Org. Syn. Coll. Vol. **4**, 552 (1963).

84. J. Berson in "Molecular Rearrangement," Vol. 1, Ed. P. de Mayo, Interscience N.Y., 1963, pp. 111-231

85. P.H. Gore, J.A. Hoskins, and S. Thorburn, J. Chem. Soc., B, 1343 (1970).

86. J.K. Groves and N. Jones, Tetrahedron Letters, 1161 (1970).

87. R.R. Sobti and S. Dev, Tetrahedon Letters, 2893 (1967).

88. P. Chamberlain, M.L. Roberts, and G.H. Whitham, J. Chem. Soc., B, 1374 (1970).

89. B.N. Blackett, J.M. Coxon, M.P. Hartshorn, B.L.J. Jackson, and C.N. Muir, Tetrahedron, **25**, 1479 (1969).

90. G. Piancatellic, A. Scettri, and M. D'Auria, Synthesis, 245 (1982).

91. R.H. Wollerberg and S.J. Miller, Tetrahedron Letters, 3219 (1978).

92. M. Cerny and J. Malek, Tetrahedron Letters, 1739 (1969).

93. A.R. Bassindale and T. Stout, Tetrahedron Letters, 3403 (1985).

94. K. Heusler, P. Weiland, and Ch. Meystre, Org. Synth., 45, 57 (1965).